

Topically applied opioids for the management of painful cutaneous ulcers in a palliative care setting

Giovambattista Zeppetella

Thesis for MD (Res)

Cancer Pharmacology Group
Centre for Experimental Cancer Medicine
Medical Oncology Laboratory
3rd Floor John Vane Science Centre
Bart's & the London School of Medicine & Dentistry
Charterhouse Square
London EC1M 6BQ

Abstract

Introduction

Painful cutaneous ulcers are a clinical challenge as the pain can be difficult to control, frequently requiring a combination of pharmacological and non-pharmacological measures. There is evidence suggesting topical opioid application might be efficacious in the management of painful cutaneous ulcers, however this is largely based on case reports.

Methods

A series of clinical and laboratory studies were undertaken to determine the utility of opioids applied topically to painful cutaneous ulcers, these included surveys of hospice admissions to determine the prevalence of painful ulcers and the effective dose of topical opioid; a randomised, double-blind, placebo-controlled crossover trial design to assess the utility of morphine/IntraSite gel mixture, HPLC analysis to determine the mixture's bioavailability and physical stability, and microbiological studies to determine its microbiological stability.

Results

A survey of 323 hospice admissions over a two-year period identified 125 patients with 221 ulcers, mostly caused by either pressure (183 ulcers) or trauma (25); 147 (67%) of all ulcers were painful. Compared to placebo, morphine/IntraSite mixture was more efficacious; it was safe and well tolerated in this population. Morphine applied topically appears to have an analgesic effect even at low doses of morphine irrespective of background analgesic medication. HPLC analyses suggested morphine and its metabolites might be detectable in the plasma of patients with large ulcers, but only at low concentrations. In addition morphine/IntraSite gel mixture was physically and, under certain storage conditions, microbiologically stable for 28 days allowing the mixture to be prepared and stored before use.

Conclusions

The studies confirmed that painful cutaneous ulcers are a significant clinical problem in hospice patients and that morphine/IntraSite mixture can be used safely and effectively in this patient group. Bioavailability studies support the possibility that the opioid analgesic effect is local rather than systemic, and stability studies show the morphine/IntraSite combination, once mixed, can be stored for up to 28 days, allowing the mixture to be prepared and stored before use. Given that ulcers can vary in aetiology, size, severity and temporal characteristics of pain, an individualised titration protocol is recommended. Further research is required to confirm and extend these findings to other ulcers and clinical settings.

Contents

Abstract	2
Declaration	7
Figures	8
Tables	12
Abbreviations	14
Acknowledgements	15
Chapter 1: Introduction	16
1.1 Cutaneous ulcer: scope of the problem	16
1.2 Cutaneous ulcers in a palliative care setting	20
1.2.1 Pressure ulcers	20
1.2.2 Malignant wounds	26
1.3 A palliative care approach	28
1.3.1 Wound pain	28
1.4 Summary	35
Chapter 2: The utility of opioid pharmacotherapy for painful cutaneous ulcers	36
2.1 Discovery and development of opioid pharmacotherapy	36
2.2 Topical opioids on cutaneous ulcers: previous studies	43
2.2.1 Methods for literature review of use of topical opioids on cutaneous ulcers	44
2.2.2 Results of literature searches	45
2.2.3 Summary of case reports and case series studying topical opioids on ulcers	45
2.3 Discussion	50
Chapter 3: Aims of the Thesis	56
Chapter 4: Prevalence of painful cutaneous ulcers in patients admitted to a hospice	57
4.1 Introduction	57
4.2 Aims of case review	58
4.3 Methods	59
4.4 Results	63
4.5 Discussion	68
4.6 Summary	72

Chapter 5:	Efficacy, safety, and tolerability of opioids applied topically to painful cutaneous ulcers	73
5.1	Introduction	73
5.2	Aims of efficacy studies	74
5.3	Pilot study: Methods	74
5.4	Results	75
5.5	Discussion	79
5.6	Randomised double blind controlled cross over study	81
5.6.1	Randomised double blind controlled cross over study: Methods	81
5.6.2	Results	83
5.6.3	Discussion	93
5.6.3.1	Other reports of topical opioid application to cutaneous wounds	100
5.6.4	Summary	104
Chapter 6:	Bioavailability of morphine applied topically to cutaneous ulcers	106
6.1	Introduction	106
6.2	Aims of bioavailability study	109
6.3	Methods	109
6.3.1	Pharmacokinetic assessment	110
6.4	Results	111
6.4.1	Patients	111
6.4.2	Subcutaneous morphine	112
6.4.3	Topical morphine	115
6.4.4	Adverse events	116
6.5	Discussion	116
6.6	Summary	118
Chapter 7:	Physical stability of opioids mixed with IntraSite gel	119
7.1	Introduction	119
7.2	Aims of physical stability studies	122
7.3	Materials	122
7.4	Methods	123
7.4.1	Analysis of opioids by HPLC	123
7.4.2	Gel Homogeneity	124
7.4.2	Gel stability	124
7.5	Results	126
7.5.1	Stability of morphine in IntraSite gel	126

7.5.2	Stability of diamorphine in IntraSite gel	129
7.5.3	Stability of oxycodone in IntraSite gel	134
7.5.4	Stability of hydromorphone in IntraSite gel	135
7.6	Discussion	140
7.6.1	Morphine	141
7.6.2	Diamorphine	142
7.6.3	Oxycodone	143
7.6.4	Hydromorphone	144
7.7	Summary	145
Chapter 8: Microbiological stability of morphine mixed with IntraSite gel		146
8.1	Introduction	146
8.2	Aims of microbiological stability study	147
8.3	Methods	147
8.4	Results	149
8.5	Discussion	149
8.6	Summary	152
Chapter 9: Opioids applied topically to painful cutaneous ulcers: results of introducing a titration protocol into clinical practice		153
9.1	Introduction	153
9.2	Aims of case review	154
9.3	Methods	154
9.4	Results	159
9.5	Discussion	167
9.6	Summary	170
Chapter 10: Discussion		171
Chapter 11: Conclusions		177
Chapter 12: Summary of recommendations for the management of painful cutaneous ulcers with topically applied morphine		179
12.1	Introduction	179
12.2	Assessment	179
12.3	Assess for and minimise risk factors	180
12.4	Indications for topically application of morphine	180
12.5	Preparation of topical morphine/IntraSite mixture	180

12.6	Storage	181
12.7	Titrate topically administered morphine from 10mg in 5mg steps	181
12.8	Reassessment	182
Chapter 13: References		184
Chapter 14: Publications list		210
Chapter 15: Appendices		229
15.1	The Oxford Quality Score	230
15.2	Scottish Intercollegiate Guidelines Network Grading levels of evidence for research	231
15.3	Waterlow Score Card	232
15.4	Classification of Eastern Co-operative Oncology Group Performance Status	233
15.5	Ethics approval for thesis related studies	234
15.6	Pilot efficacy study: Trial diary of patient number three to highlight problem with NRS scores	235
15.7	RCT: Trial diary of patient number one	245
15.8	Patient bioavailability data following application of morphine to cutaneous ulcers	252

Declaration

The work herein is independent work of the author, unless otherwise stated below, with guidance from the supervisor.

The concept of the thesis was that of the author who designed and undertook the systematic literature reviews, retrieved and reviewed the clinical notes and extracted data for prevalence, efficacy and titration aspects of the thesis, undertook some of the biochemical analyses in the stability and bioavailability studies and prepared all samples of the microbiological studies.

Dr Maria Ribeiro was involved in the design and analysis of the efficacy, bioavailability and morphine/diamorphine stability studies. Dr James Paul assisted in the pilot efficacy study. Ms Sue Powell was the research nurse and assisted in the second efficacy study. The Barry Reed Laboratory carried out the HPLC studies for bioavailability of morphine and stability of morphine, diamorphine, oxycodone and hydromorphone. Ms Hannah Smith was involved in the oxycodone and hydromorphone stability studies in the Barry Reed Laboratory. The Royal London Hospital Microbiology Department assisted in the microbiological stability study.

Figures

1.1	Diagram illustrating a cross section through normal skin	16
1.2	Common sites of pressure ulceration in individuals at risk of ulceration.	21
1.3	Photographic examples of pressure ulcers.	23
1.4	Photographic examples of malignant ulcers.	27
1.5	The influences on pain by wound type	30
1.6	Factors influencing an individual patient's response to an opioid	32
2.1	Endogenous opioid peptides are released by immune cells to reduce inflammatory pain. Adhesion molecules expressed on immune cells and inflamed endothelium coordinate the migration of circulating immune cells into inflamed tissue. The proinflammatory mediators corticotropin-releasing factor (CRF) and interleukin-1 β (IL-1 β), as well as the sympathetic neurotransmitter, noradrenaline, stimulate immune cells to secrete their opioid peptides. These peptides activate opioid receptors located on the peripheral ends of sensory neurons and effectively reduce inflammatory pain. Immune cells, devoid of their opioid contents, then continue their passage to neighbouring lymph nodes.	40
2.2	Studies on topical opioids and painful ulcers identified in a systematic review of the literature	46
4.1	Wound assessment chart within clinical record at St Clare Hospice describing each of the four ulcer stages	60
4.2	Wound assessment collection form used as part of clinical record at St Clare Hospice	61
4.3	Ulcer prevalence survey: Data extraction form for patient number 27 identifying three painless grade 3 sacral pressure ulcers	62
4.4	Patients admitted to a hospice inpatient with and without cutaneous ulcers, and whether or not the identified ulcers were associated with pain	67
4.5	Verbal rating score (VRS) of constant (n = 99) and transient (n = 85) pain severity from cutaneous ulcers reported by patients on admission to a hospice	67
5.1	Local adverse effects reported by the five patients during the placebo, washout and morphine phases of the pilot study	78

5.2	Study Disposition (CONSORT Diagram)	84
5.3	Randomised double blind placebo controlled cross over study ITT population (n=21): Median, upper and lower quartiles, minimum and maximum NRS at baseline and during morphine, washout and placebo treatment periods	89
5.4	Local adverse effects during the placebo, washout and morphine phases of the randomised controlled study were recorded by patients (n=15)	92
5.5	Nurses reported dressing related pain, local reactions or systemic adverse during the placebo, washout and morphine phases of the randomised controlled study in patients (n=13)	92
6.1	Diagram to illustrate the components of an HPLC system: the sample is injected into the column; the separated solutes are detected as they emerge from the columns by a sensitive detector, and the detector signal is recorded to give a quantifiable record.	108
6.2	Plasma morphine, M6G and M3G concentration in 6 patients after 10 mg subcutaneous morphine infused over 4 hours (mean + SD).	113
6.3	Plasma morphine and M6G concentrations in patient 6 after 10 mg topical morphine in IntraSite gel.	113
7.1	Chemical structure of morphine	119
7.2	Chemical structure of diamorphine	120
7.3	Chemical structure of oxycodone	120
7.4	Chemical structure of hydromorphone	121
7.5	Stability study No. 1: Chromatogram of mixed standard, morphine and diamorphine samples. Naltrexone used as internal standard	126
7.6	Stability study No. 1: Morphine stability in IntraSite gel at room temperature (dark and dark/light cycle) and at 4°C (Mean ± SD).	127
7.7	Stability study No. 2: Morphine stability at room temperature, day 28. Naltrexone used as internal standard	128
7.8	Stability study No. 2: Morphine stability in IntraSite gel at room temperature (dark and dark/light cycle) and at 4°C (Mean ± SD) between 0 and 28 days.	129
7.9	Stability study No. 1: Stability of diamorphine hydrochloride in IntraSite gel stored at 4°C (A), at room temperature in the dark (B) and dark/light (C); (Mean + SD)	130

7.10	Stability study No. 2: Stability of diamorphine hydrochloride in IntraSite gel stored at 4°C at room temperature in the dark (B) and dark/light (C); (Mean ± SD)	131
7.11	Stability study No. 2: The appearance of 6-MAM (A) and morphine (B) from diamorphine in IntraSite gel stored at different temperature and light conditions; (Mean ± SD)	132
7.12	Stability study No. 2: Diamorphine stability at room temperature (Days 1 and 28). Naltrexone used as internal standard	133
7.13	Chromatogram showing separation of the analytes for the oxycodone assay. Naloxone used as internal standard.	136
7.14	Graph of Oxycodone concentration over time in gels stored at each condition; (Mean ± SD)	136
7.15	Chromatogram showing unknown peak in the oxycodone gel sample stored at room temperature in day/night conditions. (day 0 and day 4 contain internal standard, Naloxone at 3.5 minutes).	137
7.16	Chromatogram showing unknown peak in the oxycodone 1.2 mg/mL QC sample on day 0, 4, 10, 21 & 28 (day 0 and day 4 contain internal standard, Naloxone at 3.5 minutes).	138
7.17	Graph of hydromorphone concentration over time in all storage conditions.	139
7.18	Chromatograms of hydromorphone 2.0 mg/mL standard on day 0, 4, 10, 21 and 28.	140
8.1	IntraSite Gel Capsule (Smith & Nephew Healthcare Ltd) containing 8g of gel	147
9.1	Topical opioid treatment protocol: front sheet with instructions for clinical staff when considering topical opioid treatment for painful cutaneous ulcers	157
9.2	Topical opioid treatment protocol: clinical documentation sheet to record ulcer characteristics, pain severity, analgesia effectiveness and whether patient chooses to change opioid dose	158
9.3	Review of clinical protocol for the titration of topically applied opioids: Morphine doses that patients deemed successful	164
9.4	Review of clinical protocol for the titration of topically applied opioids: Relationship between successfully titrated topical morphine dose and patients' regularly scheduled opioid analgesia	164
9.5	Review of clinical protocol for the titration of topically applied opioids: Pre and post titration pain NRS (mean ± SD) for background and transient pains.	165

9.6	Review of clinical protocol for the titration of topically applied opioids: Morphine doses for patients requiring the longest titration periods	160
12.1	Topically applied morphine to painful cutaneous ulcers: management algorithm	183

Tables

1.1	Categories of cutaneous ulcers.	18
1.2	Risk factors for delayed wound healing.	19
1.3	Elements of a comprehensive wound assessment	19
1.4	Pressure ulcer classification.	25
1.5	Problems arising from malignant wounds.	29
1.6	Types of dressing used in the management of chronic wounds, their description and types of use	33
2.1	Opioid receptors, their ligands, locations, and responses mediated by them	38
2.2	Studies identified in the systematic literature review	47
4.1	Characteristics of patients admitted to a hospice according to whether or not they had cutaneous ulcers	65
4.2	Duration and physical characteristics of ulcers identified in patients admitted to a hospice	65
4.3	Statements for the assessment and management of persistent (chronic) and total wound pain	71
5.1	Characteristics of patients recruited to a pilot double blind placebo controlled cross over study	75
5.2	Pilot double blind placebo controlled cross over study: Patient numerical rating score (NRS) following morphine and placebo administered topically to painful ulcers and NRS during washout period	76
5.3	Characteristics of patients recruited and randomised to the double blind placebo controlled cross over study	85
5.4	Randomised double blind placebo controlled cross over study: NRS at baseline and during morphine, washout and placebo phases	87
5.5	Studies identified in the updated systematic literature review (2002-2010)	96
6.1	Morphine bioavailability study: patient and ulcer characteristics	112
6.2	Pharmacokinetics and bioavailability data for subcutaneous and topically administered morphine in all study patients	114
6.3	Pharmacokinetics of morphine and its glucuronides following subcutaneous and topical administration of morphine sulphate	115
8.1	Results of microbiological analysis of morphine sulphate mixed with IntraSite gel at stored in three storage conditions: samples tested at Days 0, 7, 14 and 28	149

8.2	Select <i>Corynebacterium</i> species associated with disease	150
9.1	Characteristics of all patients commenced on the titration protocol for topically applied opioid	160
9.2	Changes on pre and post titration morphine dose	162

Abbreviations

6-MAM	6-mono-acetylmorphine
ACN	Acetonitrile
AUC	Area under the concentration time curve
Cmax	Maximum Concentration
ECOG	Eastern Co-operative Oncology Group
GDP	Guanosine diphosphate
GTP	Guanosine triphosphate
HPLC	High Performance Liquid Chromatography
ITT	Intention to treat
LLQ	Lower limits of quantitation
M3G	Morphine-3-glucuronide
M6G	Morphine-6-glucuronide
MST	Morphine sulphate tablet
NRS	Numerical Rating Scale
NSAID	Non-steroidal anti-inflammatory drug
PO	Per Os (orally)
RCT	Randomised Controlled Trial
SC	Subcutaneously
TELER	Treatment Evaluation by the LE Roux method
Tmax	Time to Maximum Plasma Concentration
VAS	Visual Analogue Scale
VRS	Verbal Rating Scale
WHO	World Health Organization

Acknowledgements

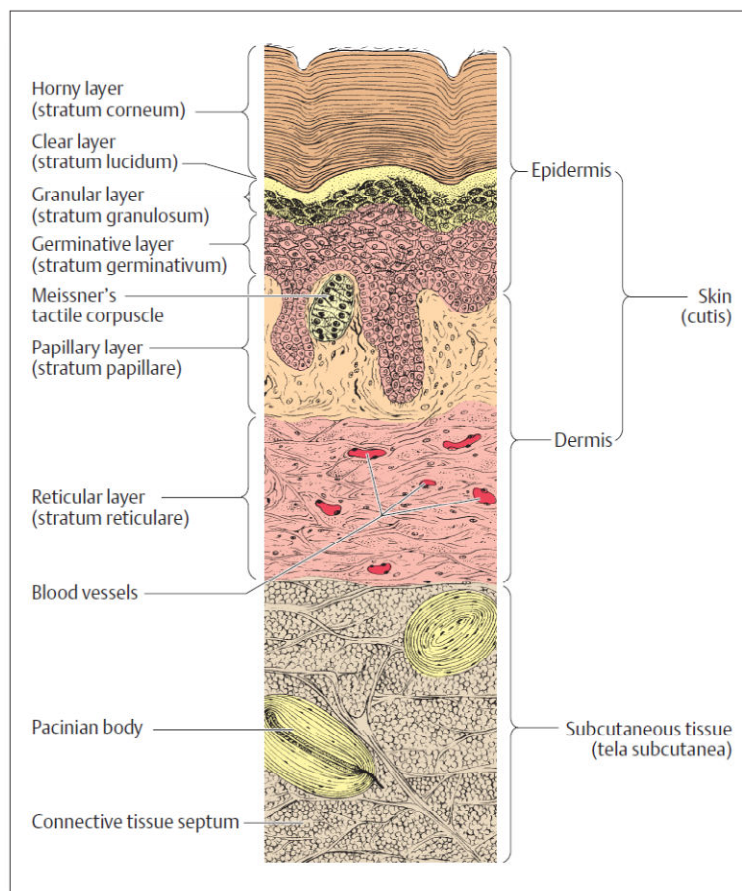
- Dr Simon Joel, Reader in Cancer Pharmacology, Barts Cancer Institute Queen Mary University of London
- Dr Joy Ross, Consultant Palliative Medicine, Royal Marsden & Royal Brompton Palliative Care Service
- Dr Robert J. Carver and Dr John Marshall from Barts Cancer Institute who provided assistance and advice in the absence of Dr Simon Joel.
- Dr Maria Dulce Correia Ribeiro, previously Medical Director and Consultant in Palliative Medicine Peace Hospice
- Clinical staff and patients at St Joseph's and St Clare Hospices for their co-operation and support with the clinical studies
- St Joseph's and St Clare Hospices for funding physical stability and bioavailability studies
- St Clare Hospice for their contribution to the funding of the microbiology stability studies
- Barry Reed Laboratory for their assistance with stability and bioavailability studies
- The Royal London Hospital Microbiology Department for microbiological testing.
- Pauline Hayward, Ruth Clements and Dave Steer for the assistance in collecting clinical data
- BMJ Publishing Group Ltd for permission to use image in Figure 1.2
- Dr Steve Thomas, Medical Device Technical Consultant/Medical Writer for permission to use images in Figures 1.3 a, b, c, d and 1.4a
- www.doctors.net.uk for permission to use the image in Figure 1.4b
- John Wiley and Sons for permission to use Figure 1.5
- Dove Medical Press for permission to reproduce Figure 2.1
- Dr Ian Back, Consultant Palliative Medicine, Cardiff, for his advice regarding the protocol for the pilot efficacy study
- Elsevier and Sage publishers for permission to reproduce the publications arising from this work

Chapter 1: Introduction

1.1 Cutaneous ulcer: scope of the problem

Skin is the largest organ of the body covering, in an average adult, an area of 1.7m^2 and weighing about 15% of the total body weight (Zaidi & Lanigan 2010). The skin consists of epidermis, the dermis, and beneath it the subcutaneous tissue [Figure 1.1].

Figure 1.1 Diagram illustrating a cross section through normal skin (Faller & Scheunke 2004)



The epidermis is a stratified squamous keratinized epithelium that in most areas of the body is 0.1–0.2 mm thick, but on the palms of the hands and the soles of the feet, 0.8–1.5 mm thick. It consists of several cell types cells, about 95% are keratinocytes, and the other prominent cells are melanocytes, Langerhan cells, and Merkel cells. The epidermis does not have any blood vessels and obtains its nutrients via diffusion from the blood vessels of the dermis. The dermis

gives skin its resistance to tearing and its plasticity. It consists of a thick network of collagen and elastic fibres and contains blood vessels, lymphatics, nerve fibres, connective tissue cells, and immune cells. The subcutaneous tissue consists of loose, adipose connective tissue, which is subdivided by bands of connective tissue. It connects the skin with the superficial fascia covering the body and enables the skin to slide over it. Between the subcutaneous tissue and the skin runs a network of arteries and veins, which sends branches as far as the dermal papillae of the dermis (Faller & Schuenke 2004).

In normal skin the epidermis and dermis exists in steady-state equilibrium, forming a protective barrier against the external environment. Once the protective barrier is broken, the complex and dynamic normal process of wound healing is set in motion to restore cellular structures and tissue layers. The process of healing can be divided into four phases: (i) coagulation and haemostasis; (ii) inflammation; (iii) proliferation; and (iv) wound remodelling with scar tissue formation (Velnar et al. 2009). However, the normal process of healing is susceptible to interruption or failure remaining in a prolonged inflammatory state characterised by elevated levels of pro-inflammatory cytokines, and abundant inflammatory cells (especially neutrophils and macrophages) which release high levels of reactive oxygen species (Wlaschek & Scharffetter-Kochanek 2005) and multiple classes of proteases (matrix metalloproteases, elastase, plasmin) (Trenkove et al. 1999). Among the causes of impaired wound healing are malnutrition; impaired blood flow and oxygen delivery; impaired inflammatory and immune responses; infection, wound separation, and foreign bodies; and age effects (Guo & Di Pietro 2010).

A cutaneous wound signifies a break in the continuity of tissues covering the body that is usually associated with a loss of substance. Deeper injuries that involve the muscle tissue, the skeletal system or internal organs are defined as complicated wounds. Wounds are

distinguished into different types depending on their cause, depth and extent of the defect: mechanical or traumatic wounds, thermal and chemical wounds or ulcer wounds.

A cutaneous ulcer is a breach in the epidermis or dermis resulting from trauma or pathological change that initiates a process of repair (Collins et al. 2002). Cutaneous ulcers, which may be acute or chronic, are a heterogeneous group with different aetiologies [Table 1.1].

Table 1.1 Categories of cutaneous ulcers

Cause	Examples
Infections	Bacterial, viral, fungal, protozoal
Vascular	Venous, arterial, vasculitis, lymphatic
Neuropathic	Diabetes, peripheral neuropathy
Haematological	Polycythaemia rubra vera, sickle cell anaemia
Traumatic	Burns, cold injury, pressure sore, radiation
Neoplastic	Basal or squamous cell carcinoma, melanoma, metastatic disease
Others	Sarcoidosis, tropical ulcer, pyoderma gangrenosum

Risk factors for delayed healing are shown in Table 1.2 (European Wound Management Association 2004). Franks et al. (1995) identified ulcer size, ulcer pre-treatment duration and limb mobility as three major factors that can delay ulcer healing, the study also demonstrated an association between social factors (social class, central heating, being male and being single) and venous ulcer healing. Others have also discussed the influence that socio-economic factors, through an association with general health, nutritional status and adherence to treatment, may adversely affect healing rates (Vetter & Matthew 1999).

In order to distinguish between the possible aetiologies a detailed clinical history should include information on the duration of ulcer, previous ulceration, history of trauma, family history of ulceration, ulcer characteristics (site, pain, odour and exudate or discharge), limb

Table 1.2 Risk factors for delayed wound healing (European Wound Management Association 2004)

Ulcer duration >6 months

Ulcer size >10cm²

Reduced mobility

Severe pain

Psychological factors

Male gender

Poor general health.

temperature, underlying medical conditions (for example, diabetes mellitus, peripheral vascular disease, ischaemic heart disease, cerebrovascular accident, neuropathy, connective tissue diseases (such as rheumatoid arthritis), varicose veins, deep venous thrombosis, previous venous or arterial surgery, smoking, medications, and allergies to drugs and dressings. Some basic features of the wound should be documented [Table 1.3] and appropriate investigations including measurement of blood pressure, weight, and urinalysis should be carried out (Grey 2003a).

Table 1.3 Elements of a comprehensive wound assessment (McManus 2007)

Wound size

Characteristics of wound edge

Location of wound

Wound base

Presence of necrotic tissue, slough, and eschar

Depth

Condition of surrounding skin

Infection

Pain

Regular assessment of patients and their skin is key to maintaining skin integrity or reducing skin damage. The assessment and management objectives should be appropriate to the stage of the patient's disease. Collier (2003) suggests four questions that can be helpful in the assessment process:

- What is the aetiology and location of the wound?
- How should the wound be graded using an objective grading tool?
- Based on the wound grading, what is the primary treatment objective?
- What regimen is required to achieve the identified treatment objectives?

In patients with advanced disease it is desirable to have a comprehensive wound assessment tool that supports an individualised plan of care and is linked with quality of life outcome measures.

1.2 Cutaneous ulcers in a palliative care setting

The management of chronic wounds in a palliative care setting is a clinical challenge. A number of factors can impede the ability of patients with cancer to heal including the disease process itself, the timing and invasiveness of the palliative treatments including surgery, chemotherapy and radiotherapy, and patient's nutritional status (Payne et al. 2008).

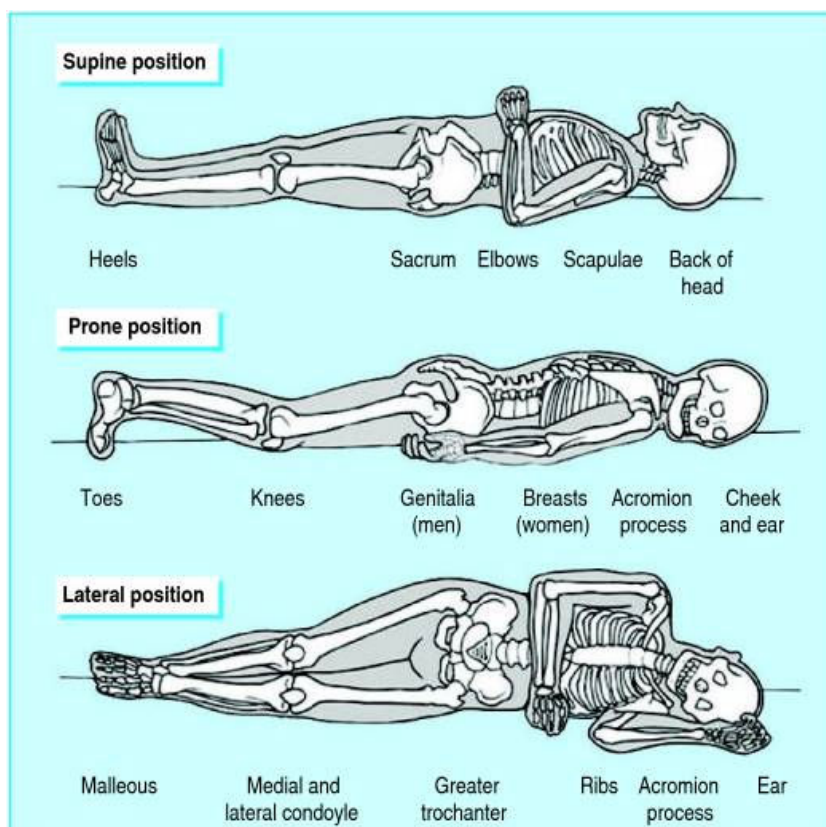
In a study of 593 patients with advanced illness, 43 types of wounds were identified and grouped into nine categories: malignant, pressure ulcers, iatrogenic, traumatic, diabetic foot ulcers, venous leg ulcers, arterial ulcers/gangrene, infections/inflammatory lesions, and ostomy related (Maida et al. 2008); the commonest causes in a palliative care setting are as a result of trauma (e.g. pressure sores) and neoplasia (Tippett 2005).

1.2.1 Pressure ulcers

Pressure ulcers are localised areas of tissue destruction occurring when soft tissue is

compressed over bony prominences for prolonged periods of time [Figure 1.2]. The prevalence in the hospice population ranges from 13 to 47% and the wounds are usually painful unless the patient is paraplegic (Langemo 2006; McDonald & Lesage 2006). Pressure ulcers represent a major burden of sickness and reduced quality of life for patients and their carers. The financial costs to the National Health Service (NHS) are also substantial (Cullum et al. 1995) and it has been estimated that preventing and treating pressure ulcers in a 600-bed general hospital costs between £600,000 and £3 million a year (Touche Ross 1993); estimates of the cost of pressure ulceration to the NHS range from £180m to nearly £2bn a year (Grey et al. 2006b). The burden has been acknowledged recently in the Department of Health's commitment to make a proportion of NHS providers' income dependant on provision of quality and innovation through Commission of Quality and Innovation Framework, which for some hospital Trusts has included the development and management of pressure sores (NHS Institution for Innovation and Improvement 2009).

Figure 1.2 Common sites of pressure ulceration in individuals at risk of ulceration (Grey et al. 2006b)



The four main factors implicated in the development of pressure sores are interface pressure, shear, friction, and moisture (Grey et al. 2006b). The wound may first present clinically with discolouration, tenderness, and changes in consistency or temperature compared to the surrounding skin (Fowler et al. 2008). Non-blanchable erythema is early evidence of abnormal perfusion due to pressure-related injury or friction or shearing forces (Vanderwee et al. 2007b). With deep tissue injury the skin may be purple or maroon, boggy or firm, and warmer or cooler than surrounding tissues [Figure 1.3 a, b, c & d]. The area may be painful and may develop blood- or serum-filled blisters. As damage evolves, the blister roof dries and an eschar develops, in time an open wound can develop of which there are different stages [Table 1.4].

Painful pressure sores are a common problem affecting a large proportion of patients in a variety of healthcare settings including palliative care settings. The pain may result from persistent and recurrent pressure-related ischaemia, trauma, shear, friction and incontinence-related skin irritation. Hatcliffe & Dawe (1996) undertook an audit of 151 patients in a UK hospice and found that 57 patients (37%) had pressure sores; 38 patients (25%) had one sore, 6 (10%) had two, 8 (5%) had three and 1 (1%) had four. Galvin (2002) retrospectively audited pressure ulcer incidence in 542 patients admitted to a specialist palliative care unit over two years and found that 26.1% were admitted with pressure ulcers while 12.0% developed pressure damage during their stay. Tippet (2005) conducted a prevalence study of chronic wounds in over 400 US hospice patients and reported 35% had a skin wound of which pressure ulcers were the most common. Reifsnnyder et al. (2004) and Reifsnnyder & Magee (2005) reported retrospective reviews of 980 patients admitted to US hospices and found the prevalence of pressure ulcers was 26.9%. Vanderwee et al. (2007a) reported that in a survey of 5947 patients in 25 hospitals in five European countries (Belgium, Italy, Portugal, UK and Sweden), 18.1% were found to have pressure ulcers of which only 9.7% received fully adequate preventive care.

Figure 1.3 Photographic examples of pressure ulcers

a. Superficial pressure sore



b. Pressure ulcer showing extent of undermining



c. Sloughy pressure ulcer



d. Necrotic pressure ulcer



Table 1.4 Pressure ulcer classification (National Pressure Ulcer Advisory Panel 2007)

Stage	Definition	Further description
I	Intact skin with non-blanchable redness of a localised area usually over a bony prominence. Darkly pigmented skin may not have visible blanching; its colour may differ from the surrounding area.	The area may be painful, firm, soft, warmer or cooler as compared to adjacent tissue. Stage I may be difficult to detect in individuals with dark skin tones. May indicate “at risk” persons (a heralding sign of risk).
II	Partial thickness loss of dermis presenting as a shallow open ulcer with a red pink wound bed, without slough. May also present as an intact or open/ruptured serum filled blister.	Presents as a shiny or dry shallow ulcer without slough or bruising. This stage should not be used to describe skin tears, tape burns, perineal dermatitis, maceration or excoriation.
III	Full thickness tissue loss. Subcutaneous fat may be visible but bone, tendon or muscle are not exposed. Slough may be present but does not obscure the depth of tissue loss. May include undermining and tunnelling.	The depth of a stage III pressure ulcer varies by anatomical location. The bridge of the nose, ear, occiput and malleolus do not have subcutaneous tissue and stage III ulcers can be shallow. In contrast, areas of significant adiposity can develop extremely deep stage III pressure ulcers. Bone/tendon is not visible or directly palpable.
IV	Full thickness tissue loss with exposed bone, tendon or muscle. Slough or eschar may be present on some parts of the wound bed. Often include undermining and tunnelling.	The depth of a stage IV pressure ulcer varies by anatomical location. The bridge of the nose, ear, occiput and malleolus do not have subcutaneous tissue and these ulcers can be shallow. Stage IV ulcers can extend into muscle and/or supporting structures (e.g., fascia, tendon or joint capsule) making osteomyelitis possible. Exposed bone/tendon is visible or directly palpable.

1.2.2 Malignant wounds

Malignant ulcers may result from local or metastatic disease that occurs on, or just below, the skin surface [Figure 1.4 a & b]. The wound may be ulcerative or proliferative and may begin with a lesion that does not heal and progresses to become a hard mass fixed to underlying structures. The tumour develops its own blood supply, which it may outgrow, resulting in a central area of necrosis. After skin breakdown occurs, the colour may range from pink to red, violet, brown, or flesh-coloured. Growth may be rapid, with a cauliflower-like lesion or ulceration. The necrotic tissue becomes a medium for anaerobic bacteria to proliferate. Disrupted microcirculation and impaired coagulation predispose to local bleeding. Sinus tracts or fistulas can be associated with deeper wounds. (McDonald & Lasage 2006).

Malignant wounds are most often associated with cancer of the breast, with an incidence ranging from 39% to 62%. The other common sites include head and neck, 24%-33.8%; back, trunk, or abdomen, 1%-3%; groin or axilla 3%-7.4%; genital, 3%-5.1%; and others, 3.7%-8% (Collier 1997; Wilkes et al. 2001; Naylor 2002).

The quality of life of patients with malignant wounds is often severely negatively affected by the production of copious exudate (due to the destruction of lymph vessels and nodes), malodour (from the high bacterial growth), itching, the constant risk of haemorrhage (due to erosion of blood vessels) and pain (Benbow 2009). It is estimated that 5% to 10% of patients with advanced cancer will develop a fungating wound (Hasfield-Wolf & Rund 1997), many of which will be painful (Hasfield-Wolfe & Baxendale-Cox 1999).

Figure 1.4 Photographic examples of malignant ulcers.

a. Fungating breast wound



b. Squamous cell carcinoma of scalp



1.3 A palliative care approach

The ideal method of providing pain relief is healing of the ulcer but in a palliative care setting this is often difficult in benign pressure ulcers and unlikely in malignant ulcers (Alvarez et al. 2002; Brown 2003; Galvin 2002; Henoch & Gustafsson 2003; Lund-Nielsen et al. 2005). The potential for palliative care to improve wound healing and the quality of life for patients and families living with chronic wounds is now increasingly recognised (Schulz et al. 2002; Ferris et al. 2007; Chrisman 2010).

Palliative care is an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual (World Health Organization 2002). As the patient's health status deteriorates the focus shifts to strategies that prioritise symptomatic relief and wound improvement ahead of wound healing (Alvarez et al. 2007); central to these palliative strategies is the use of pharmacotherapy.

The palliative care approach encompasses a number of therapeutic interventions that aim to promote wound healing, control pain, manage infection, odour, bleeding, exudate, and maintain a good quality of life for the patient and caregiver (McDonald & Lesage 2006; Maida et al. 2009) [Table 1.5]. The focus in the remainder of this introduction will be on wound pain.

1.3.1 Wound pain

Chronic wound pain is multifaceted and the pathophysiological processes may involve either tissue or nerve injury, which generally speaking can generate two different pain states; nociceptive pain from the tissue damage creating the wound and neuropathic pain from damaged peripheral nerves at the site of the wound [Figure 1.5]. Nociceptive pain results from

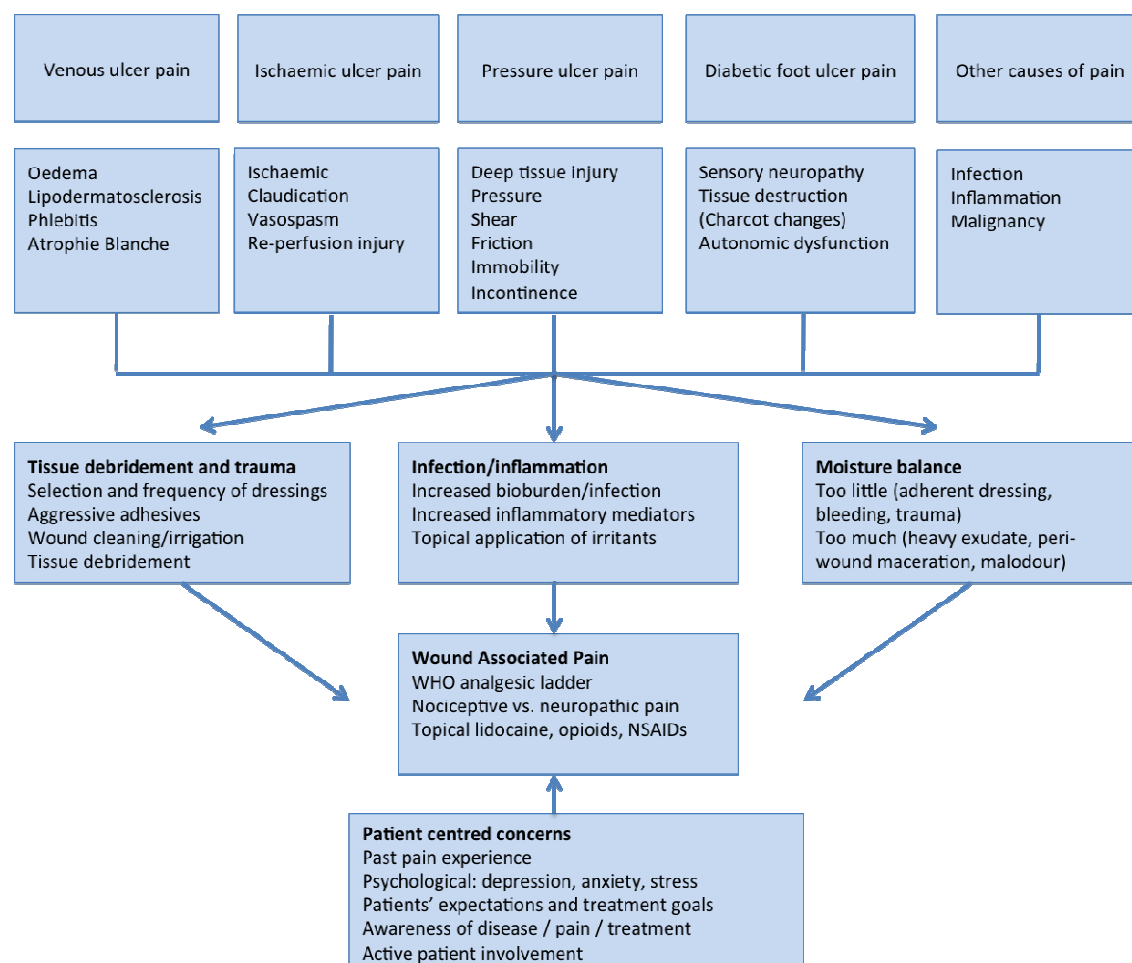
Table 1.5 Problems arising from malignant wounds (McDonald & Lesage 2006)

Problem	Nature of impact
Psychosocial	<ul style="list-style-type: none">• May include depression, anxiety, poor body image, low self-esteem, and inhibited sexuality or intimacy.• Bulky dressings can affect self-image and decrease mobility.• Patients can become isolated from family and friends because of disfigurement and odour.
Pain	<ul style="list-style-type: none">• Usually depends on the location of the wound, the depth of tissue invasion and damage, the involvement of nerves, the presence of viable tissue with exposed nerve endings, and the person's previous experience with pain and analgesia.
Exudate	<ul style="list-style-type: none">• Can vary in amount and originates from tumour secretions and increased leakage from blood vessels.
Odour	<ul style="list-style-type: none">• Odour occurs when tissue is deprived of oxygen and nutrients, becoming necrotic with bacterial growth.• Organisms commonly causing odour include anaerobes and aerobes.• Odour can be a particular problem if the malignant ulcer is close to the bowel or the anus.• Odour can cause nausea and reduced appetite, resulting in weight loss and lethargy.
Bleeding	<ul style="list-style-type: none">• Bleeding occurs because of abnormal microcirculation within the tumour, erosion of blood vessels by malignant cells, and decreased platelet function.
Itch	<ul style="list-style-type: none">• Itch is different from the irritation caused by maceration and, although there may be no obvious cause, it is thought to be related to the growth of the tumour. Successful management can be difficult.

normal function of the nervous system caused when a noxious stimulus activates A δ -fibres and C-fibres in either the cutaneous or deep tissues. Nociceptive pain may have a sharp or dull quality, is well defined and clearly located. Neuropathic pain is initiated or caused by a primary lesion or dysfunction in the nervous system. Neuropathic pain may have continuous and/or paroxysmal components and may be associated with so-called positive (e.g. allodynia, hyperalgesia, dysaesthesia and paraesthesia) and negative symptoms (e.g. hypoaesthesia, anaesthesia, hypoalgesia, and analgesia) that occur spontaneously or in response external stimuli (Bennett 2006). In one study, more than 40% of patients with leg ulcers exhibited

neuropathic pain symptoms (Briggs et al. 2008).

Figure 1.5 The influences on pain by wound type (modified from Woo et al. 2008)



It is often accepted that when there is destruction of peripheral nociceptors in the deepest wounds [Figure 1.3d], these are less painful than the more superficial wounds [Figures 1.3 a, b & c], however in patients with burns, areas of full thickness burns remained painful despite nerve destruction (Atchison et al. 1991), individualised assessment is therefore required in order to identify pain in each patient.

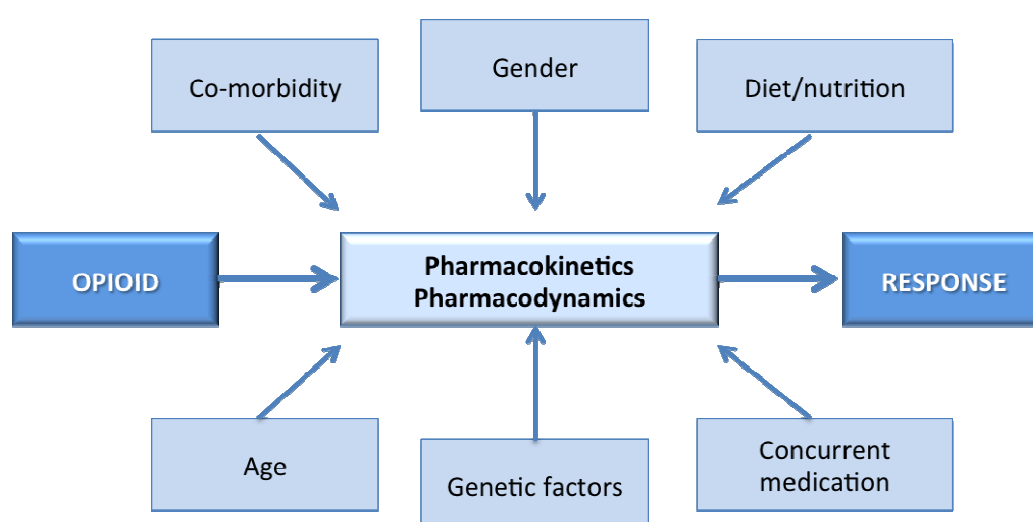
Pharmacotherapy is the cornerstone of cancer pain management, with the aim of providing the greatest pain relief possible, with the fewest number of adverse effects, using the most convenient mode of administration. The World Health Organization (WHO) analgesic ladder,

first published in 1986, provides a simple framework for the pharmacological management of cancer pain using a logical stepwise approach (World Health Organization 1986). Presented in the form of a three-step ladder, the WHO method recommends a non-opioid for mild pain at step 1, an opioid for mild to moderate pain at step 2 and an opioid for moderate to severe pain at step 3; analgesia is delivered according to the severity of the pain and not the severity of the disease. Treatment "by the individual" is a fundamental principle of the WHO ladder as an individual patient's response to a particular analgesic is determined by several factors including pain severity, previous analgesia exposure, age of the patient, extent of the cancer, and concurrent disease [Figure 1.6].

Wound-related pain is often difficult to manage, in part because it is often poorly responsive to opioids (Hanks 1991). Opioid responsiveness is the degree of analgesia achieved as the dose is titrated to an endpoint defined either by intolerable adverse effects or the occurrence of acceptable analgesia (Mercadante & Portenoy 2001). In wound-related pain this may result from several mechanisms including changing nociception associated with ulcer progression or the external trauma (e.g. shear forces) it undergoes, the presence of a neuropathic component to the pain requiring higher doses of systemic opioid to achieve acceptable analgesia and potentially resulting in greater toxicity, and the temporal pattern of the pain which has described as cyclic (periodic discomfort), non cyclic (single incident) and chronic (persistent discomfort) (Krasner 1995). Furthermore individual patients may have other reasons resulting in poor opioid responsiveness not directly related to the ulcer such as age, gender and ethnic group and the production of opioid metabolites [Figure 1.6]. These factors suggest that wound-related pain requires a thorough assessment and that successful treatment of difficult wounds requires assessment of the entire patient and not just the wound, yet the evidence suggests it is poorly assessed, documented and researched (Duncan & Brooks 2009).

In the context of wound pain, analgesia has been administered both systemically and also topically to the wound. A systematic review of the literature failed to identify any randomised controlled studies to support the utility of systemic analgesia (Evans & Gray 2005), and in many cases management has focussed on locally applied measures. However the dressing changes themselves can be a cause of pain as highlighted in an international survey of 11 countries (European Wound Management Association 2002).

Figure 1.6 Factors influencing an individual patient's response to an opioid (Dickman 2010)



A number of dressings are available [Table 1.6] and ideally should offer non bulky comfort sized to the wound, gentle adherence, cost-effectiveness, a moist wound healing environment, minimisation of shear, friction and pressure, impermeability to bacteria, long wear time, absorbency of excess exudate to prevent skin excoriation and ease of dressing use by patient or care-giver (Grocott 2007; McDonald & Lasage 2006; Reddy et al. 2003; Whitney et al. 2006; Robson et al. 2006). A systematic review of the evidence of the effects of dressings and topical agents on quality of life, and symptoms that impact on quality of life, in people with fungating malignant wounds identified only two trials (63 people), one of which provided weak evidence that 6% miltefosine solution applied topically to superficial fungating breast lesions (smaller than 1 cm) in patients who have received either previous radiotherapy, surgery, hormonal

Table 1.6 Types of dressing used in the management of chronic wounds, their description and types of use (Worley 2011)

Dressing type	Description	Types of uses
Transparent films	Usually polyurethane membranes coated with an adhesive that will not stick to the wound bed. Unable to absorb drainage but can protect superficial wounds	Skin tears – re-approximate wound edges prior to application Friction injury
Hydrocolloids	Hydrophilic particles that are bound within a matrix. Outer layer is usually a thin film or polyurethane foam. Absorb drainage by particle swelling	Ruptured blisters or bullae - use caution when removing Use on wounds with small to moderate amounts of drainage, partial-thickness pressure ulcers, venous leg ulcers, or arterial ulcers. Exercise caution when removing as adhesives are strong
Hydrogels	Predominantly water-based, dressings are either amorphous (gel form) or bound in an inert matrix (sheet form). Not particularly absorbent due to high water content	Provide soothing and cooling benefit May be used on partial-thickness wounds, wounds from ionizing radiation, itching
Foams	Usually made from polyurethane polymers that are hydrophilic and absorptive. Available in adhesive and non-adhesive forms	Use on small to moderately draining wounds, depending upon thickness, Pressure ulcers, Skin tears, Traumatic injuries, Lower extremity ulcers
Alginates	Derived from seaweed fibres, these dressings are capable of managing larger amounts of drainage	Use on wounds with moderate to heavy drainage. Requires secondary dressing
Composite dressings	These dressings are “combination” products made from two or more materials which are physically distinct but manufactured together	Use as cover dressings to assist with drainage management or as single dressings over tube sites or IV lines. The amount of wound exudate will determine the appropriate composite dressing
Contact layers	These dressings are designed to prevent adhesion of dressing materials to the wound bed. May be woven or nonwoven	Use for packing painful wounds
Antimicrobial dressings	Available in both pad and gel form, these dressings are designed to control bacteria present in wounds – may contain substances such as cadexomer iodine, silver, or polyhexamethylene	Use on wounds with significant colonization or bio-burden and are often used in combination with other dressings

therapy or chemotherapy for their breast cancer, may slow disease progression (Adderley & Smith 2007). Furthermore dressing products that are designed to heal acute wounds may not have the same effect on chronic, non-healing wounds (Enoch & Price 2004).

In some cases medication applied topically to the wound has been found to be beneficial. A systematic review identified six randomised controlled trials showing that 5% Eutectic Mixture of Local Anaesthetics (EMLA) lidocaine and prilocaine mixture versus placebo significantly reduced the pain intensity during and after sharp debridement of leg ulcers as determined by visual analogue scale (VAS) pain score (Briggs & Nelson 2010). Lidocaine patches applied to painful areas worn for a maximum of 12 hours daily have been reportedly effective (Evans & Gray 2005).

Other analgesics have been applied topically to painful wounds. Ibuprofen, for example, has been incorporated into a foam dressing that in the presence of exudate is continuously released throughout the entire wear time. Positive results have been reported as case series (Flanagan et al. 2006) and crossover case series (Jorgensen et al. 2006) and in three randomised controlled studies (Gottrup et al. 2008; Romanelli et al. 2008; Palao i Domenech et al. 2008). However a Cochrane systematic review concluded there was no evidence, on the basis of two of the randomised trials, that foam dressings containing ibuprofen significantly reduce venous leg ulcer associated pain; the trial by Palao i Domenech et al. (2008) was published after the review.

Topical anaesthetics such as lidocaine are occasionally used for pain associated with pressure ulcers but rarely for the pain associated with malignant skin ulcers. The complex nature of these wounds usually requires specialised dressings [Figure 1.6] making it difficult to apply anaesthetics directly to them; the same is true of commercially available topical NSAID

formulations. This, together with the lack of evidence for these treatments, has led to an alternative approach. What dressing can be safely applied to a wide variety of wounds and what type of analgesic can be placed within it?

Opioids have also been used in an effort to achieve localised pain relief. Although a recent review of topical analgesics included transdermal preparations of both fentanyl and buprenorphine as topical opioids, these formulations are applied topically for a systemic rather than a local effect (Moody 2010). In contrast other studies have reported a localised effect. In one such study a mixture of 120 mg morphine in 80 grams of a moisturizing cream was applied topically for painful back conditions in 26 patients. From 1 mg to 3 mg was applied daily and treated with ultrasound to enhance penetration. Most patients (88%) noted up to 40% or 50% localized pain relief for four or more hours, and 19% reported relief lasting longer than a day (Tennant et al. 1993) However it is the direct application of an opioid directly onto an open wound that has gained most interest in an effort to provide local analgesia and minimise systemic adverse effects (Back & Finlay 1995; Krajnik et al. 1999). Topically applied morphine, for example, has been reported as providing rapid pain relief which lasted usually for seven to eight hours with no, or minimal, adverse effects (Krajnik et al. 1999). The theories on the possible mechanisms of actions are discussed further in Chapter 2.

1.4 Summary

Painful cutaneous ulcers as a result of trauma or malignancy are a frequent problem in a palliative care setting. They can be extremely debilitating leading to considerable patient suffering and morbidity. For some palliative care patients with wounds, treatment of the underlying condition will result in full or partial wound healing using best practice wound care. For those where chronic wounds persist, integrating the principles of palliative care that provide the patient the most comfort in controlling symptoms, such as pain may be beneficial.

Chapter 2: The utility of opioid pharmacotherapy for painful cutaneous ulcers

2.1 Discovery and development of opioid pharmacotherapy

Comprehensive cancer care includes the effective management of pain where pharmacotherapy is the cornerstone of treatment, with the aim of providing the greatest pain relief possible with the fewest number of adverse effects using the most convenient mode of administration. An effective pain control strategy for an individual patient requires knowledge of the way in which the cancer, the cancer treatment and the pain therapy interact (Vascello & McQuillan 2006). Opioids are commonly used analgesics, in particular morphine (Klepstad et al. 2005).

Morphine was first isolated from unripe seed pods of opium poppy, *Papaver somniferum* in 1803 by a German pharmacologist Friedrich Sertürner who named it morphium after the Greek god of dreams, Morpheus. The opium poppy had been cultivated as early as 3400 BC in lower Mesopotamia where the Sumerians referred to it as “Gil,” (“happiness”) (Schiff 2002). The farming practice passed to the Assyrians and then the Babylonians who in turn passed their knowledge onto the Egyptians; ancient papyrus records reported the use of opium for pain relief (Breasted 1930).

The structure of morphine was first determined in 1925 (Gulland & Robinson 1925) and the molecule eventually synthesised in 1952 (Gates & Tschudi 1952). Its rigid characteristics led to the theory that the analgesic effects are produced by interaction with specific receptors (Beckett & Casey 1954). In 1973 using radioactive morphine the drug was found to attach to very specific areas of the brain, dubbed “morphine receptors” (Pert & Snyder 1973; Simon et al. 1973; Terenius 1973) which triggered a search for the molecule that would endogenously

stimulate that receptor, culminating in the discovery of “endogenous morphines” or “endorphins” (Hughes et al. 1975). The existence of multiple opioid receptors had been proposed (Portoghese 1965; Gilbert & Martin 1976; Martin et al. 1976) and subsequent pharmacological studies led to the classification of opioid binding sites into three receptor classes referred to as delta (δ), kappa (κ) and mu (μ) receptors each encoded by separate structural genes (Goldstein 1987; Pasternak 1993). The cloning of the opioid receptors and subsequent use of recombinant DNA technology has greatly advanced our understanding of their structure and function (Minami & Satoh 1995).

Opioid receptors belong to the G-coupled receptor super family of transmembrane proteins that are present in both spinal and supra-spinal levels of the central nervous system. There are more than 20 types of G-protein and different receptors appear to interact preferentially with different types of G-protein (Gudermann et al. 1999). The receptors consist of an extracellular N-terminus, seven transmembrane helical twists, three extracellular and intracellular loops, and an intracellular C-terminus. The proteins are heterotrimeric consisting of α , β , and γ subunits that when activated triggers their immediate phosphorylation, exchanging its bound guanosine diphosphate (GDP) for a guanosine triphosphate (GTP), followed by uncoupling from intracellular G proteins and sequestration (Carman & Benovic 1998). Both the GTP bound α subunit and the combined $\beta\gamma$ units can initiate steps in the signalling pathway.

Opioid receptors are present in several regions of the central nervous system that are involved in nociception [Table 2.1]. Activation of any of the three opioid receptor subtypes from both endogenous and exogenous opioids produces common cellular actions including the inhibition of adenylyl cyclase, activation of a potassium conductance, inhibition of calcium conductance, and an inhibition of transmitter release (Zöllner & Stein 2007). The pharmacodynamics response to an opioid depends upon the receptor to which it binds its affinity for that

receptor, and whether the opioid is an agonist or an antagonist.

Table 2.1 Opioid receptors, their ligands, locations, and responses mediated by them (Koneru et al. 2009)

Receptor	Endogenous ligand	CNS Location	Response on activation
μ	Endorphins	Brain (laminae III and IV of	μ 1-supraspinal analgesia,
	Endomorphins	the cortex, thalamus, periaqueductal gray), spinal cord (substantia gelatinosa)	μ 2-Respiratory depression, miosis, euphoria, reduced gastrointestinal motility
κ	Dynorphin A	Brain (hypothalamus, periaqueductal gray, claustrum), spinal cord (substantia gelatinosa)	Spinal analgesia, sedation, miosis, inhibition of antidiuretic hormone release
δ	Enkephalins	Brain (pontine nucleus, amygdala, olfactory bulbs, deep cortex)	Analgesia, euphoria

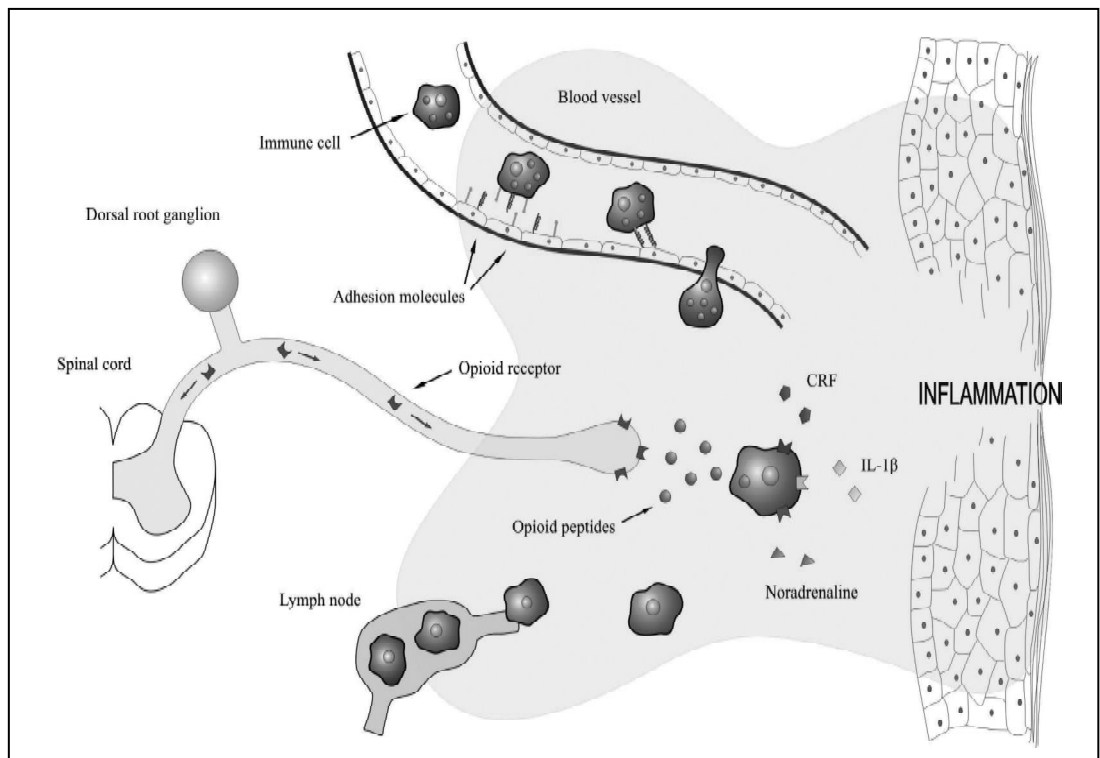
Opioids may act on either presynaptic nerve terminals or postsynaptic neurones and produce their effects through reduced excitability of nerve terminals, attenuation of action potentials inhibition of excitatory neurotransmitters and increased transmission of the descending inhibitory pathways. Traditionally opioids have been considered to have a site of action in the central nervous system, however the analgesic actions of topical opioids were noted in the eighteen and nineteenth century. In 1774 William Herberden wrote that patients with haemorrhoids should ‘apply a mixture of a dram of the softened extract of opium mixture and any simple ointment for pain so excessive so as to require immediate effect (Heberden 1962). As the usual adverse effects were not observed, he speculated whether opium acted ‘as a topical anodyne’. In 1885 Wood documented that morphine elicited analgesia when administered topically to painful sites in the peripheral tissues (Wood 1885). Opioid receptors have now been demonstrated on peripheral nerves and lymphocytes (Fields et al. 1980; Hassan et al. 1992; Stein 1995; Stein et al. 1995; Zhou et al. 1998) suggesting that opioids may have additional peripheral analgesic effects.

All classes of opioid receptors have been demonstrated on peripheral nerve terminals, and are similar to the population of receptors found in the central nervous system (Stein 1995). Opioid receptors are not obvious in normal tissue but become evident within minutes to hours after the start of inflammation. The expression and upregulation of opioid peptides and their precursors and processing enzymes has been demonstrated in both animals (Sitte et al. 2007) and humans (Mousa et al. 2007). Opioid receptor mRNA transcription is apparently upregulated by electrical neuronal activity in response to the nociceptive input from the inflamed tissue, as this effect can be abolished by a local anaesthetic nerve block (Puehler et al. 2004). Once upregulation occurs, opioid receptors are transported peripherally resulting in a higher density of opioid receptors at peripheral nerve terminals (Stein et al. 2003; Mousa et al. 2007); this stimulation results from the actions of cytokines and nerve growth factor from the inflamed tissue.

In addition to dorsal root ganglia and peripheral sensory nerves, opioid receptors have been identified on lymphocytes, macrophages and mast cells (Antonijevic et al. 1995; Coggeshall et al. 1997); hence analgesia can be elicited by endogenous opioid peptides released from immune cells at the site of inflammation (Machelska et al., 2002; Stein et al. 1993).

Inflammation rapidly stimulates immune cell extravasation and migration into injured tissues and in early inflammation; granulocytes (especially neutrophils) are the major opioid-containing leukocytes, whereas in later stages of inflammation, monocytes or macrophages and lymphocytes predominate (Rittner et al. 2008; Stein et al. 2003). Opioid peptide is released from the immune cells upon stimulation with corticotropin-releasing factor, noradrenaline, tumour necrosis factor alpha, and interleukin-1beta and the immune cells return to the local lymph node depleted on peptide (Binder et al. 2004; Czlankowski et al. 1993; Sehgal et al. 2011).

Figure 2.1 Endogenous opioid peptides are released by immune cells to reduce inflammatory pain. Adhesion molecules expressed on immune cells and inflamed endothelium coordinate the migration of circulating immune cells into inflamed tissue. The proinflammatory mediators corticotropin-releasing factor (CRF) and interleukin-1 β (IL-1 β), as well as the sympathetic neurotransmitter, noradrenaline, stimulate immune cells to secrete their opioid peptides. These peptides activate opioid receptors located on the peripheral ends of sensory neurons and effectively reduce inflammatory pain. Immune cells, devoid of their opioid contents, then continue their passage to neighbouring lymph nodes.



Reprinted from Therapeutics and Clinical Risk Management, Volume 1, Kapitzke D, Vetter I, Cabot PJ, Endogenous opioid analgesia in peripheral tissues and the clinical implications for pain control pp279-297, 2005, with permission from Dove Medical Press Ltd

The central and peripheral analgesic systems are not independent of one another and there is evidence, for example, that the migration of opioid-containing leukocytes into injured tissue can be modulated by central mechanisms. Schmitt et al. 2003 demonstrated that analgesic doses of intrathecally administered morphine decreased the number of β -endorphin

containing leukocytes in inflamed rat paws. The finding was confirmed by Heurich et al. 2007 administering epidural analgesia in patients undergoing surgery. It appears, therefore, that effective central inhibition of pain reduces the recruitment of opioid-containing cells to injured tissues suggesting at least two possible mechanisms (peripheral and central) to respond to pain resulting from peripheral injury.

The confirmation that peripheral opioid receptors exist has led to the possibility of specific pharmacological targeting of them. The potential advantages of delivering opioids peripherally, for example by topical application, includes maximising opioid concentration at the site of pain, lower plasma levels with potentially fewer adverse effects and fewer drug interactions. Although targeting peripheral analgesics mechanisms may reduce the central adverse effects of systemic opioid analgesics, peripherally mediated side effects may remain problematic resulting from opioid receptor expression on peripheral nervous system neurons innervating peripheral organs such as skin and gastrointestinal tract (Bagnol et al. 1997; Fickel et al. 1997; Bigliardi-Qi et al. 2004; Holzer 2004). For example mu-opioid receptors have been found to be expressed in the gut from the stomach through to the distal colon where their function is thought to include control of visceral pain, regulation of transit time of luminal contents, and mucosal transport of fluids and electrolytes. The effect of opioid receptor agonists on gut motility and secretion has been utilized clinically in the symptomatic management of diarrhoea (Sun et al. 1997). Opioid receptor proteins have also been described in several non-neuronal tissues such as vascular and cardiac epithelia although the significance of this is unclear (Bildack 2000; Cadet et al. 2000; Mousa et al. 2001; Bigliardi-Qi et al. 2004).

A number of studies have investigated the local analgesic effects of opioids in the clinical setting. Studies have examined buccal, dental, perineural, and regional intravenous administration, mostly in the postoperative setting and have produced conflicting results

(Cerchietti et al. 2002; Dionne et al. 2001; Racz et al. 1991; Gustafsson et al. 1988); most studies have looked at intra-articular opioid administration (Kalso et al. 1997; Gupta et al. 2001; Kalso et al. 2002).

Kalso et al. (1997) systematically reviewed randomised controlled trials on intra-articular opioids and identified 36 studies in knee surgery. Six had both a local anaesthetic control and placebo and four showed internal sensitivity, all of which had at least one outcome showing efficacy of intra-articular morphine against placebo. Of the six studies comparing intra-articular morphine with intravenous or intramuscular morphine or with intra-articular saline without a bupivacaine control, four showed greater efficacy for intra-articular morphine; no dose-response was evident. They concluded that intra-articular morphine might have some effect in reducing postoperative pain intensity and consumption of analgesics, although studies had significant problems in design, data collection, statistical analysis and reporting.

Gupta et al. (2001) reviewed the literature and performed a meta-analysis of the peripheral effects of morphine injected intra-articularly to determine whether does morphine injected intra-articularly produced analgesia, was it a dose-dependent effect, and, if so, is the effect systemic or mediated via peripheral opioid receptors. Forty-five articles were identified in which the effects of morphine were studied in a prospective, randomized manner, and 32 included a placebo control. Nineteen studies were suitable for meta-analysis that showed an improvement in analgesia after morphine compared with placebo, although studies with high quality scores showed somewhat smaller improvements. There was no effect on decreased analgesic consumption and no clear dose-response effect seen when VAS was used as a measure of pain, but it was seen when area under the curve was used as a measure of pain. A systemic effect of peripherally injected morphine was not possible to exclude because of the very limited data available.

Kalso et al. (2002) identified 25 publications reporting on 28 RCTs in a systematic literature review. Twenty-seven comparisons of six different doses (1-10 mg) of intra-articular morphine vs. placebo, four comparisons on dose-response and three cross-route comparisons were included. Fifteen trials with placebo controls were considered sensitive at any time point, immediate (0-2 h), early (2-6 h) and late (6-30 h), whereas ten trials were negative for all periods. Ten out of the 12 trials that were sensitive for the late period indicated that intra-articular morphine provided significantly superior long-term post-operative analgesia. Most positive studies had used higher doses (3-5 mg) compared with negative studies that had mainly used 1 mg. The two studies using Patient Controlled Analgesia consumption of morphine as the primary outcome also showed that intra-articular morphine was superior to intra-articular saline. The authors concluded that intra-articular morphine in a dose of 5 mg seems to provide relief of postoperative pain for up to 24 hours.

In summary, some of the published studies examining intra-articular opioid administration have demonstrated opioid-specific long acting and locally specific analgesic effects, provided adequate doses are used. Effective doses were relatively low and produced plasma concentrations of opioid incapable of producing a systemic effect, hence adverse effects were uncommon. The effects were reversed by intra-articular naloxone. Those studies that failed to show an effect often demonstrated a lack of tissue inflammation.

2.2 Topical opioids on cutaneous ulcers: previous studies

The effects of opioids applied topically to painful cutaneous ulcers have been described in the palliative care setting. The aim of this systematic literature review was to identify the evidence for their clinical utility at the start of this research project. The review was later extended to included current studies in the discussion section of Chapter 5.

2.2.1 Methods for literature review of use of topical opioids on cutaneous ulcers

Published trials and case series that investigated the utility of topical opioids for painful cutaneous ulcers were included. All studies that compared topical opioid analgesics with placebo or other opioid analgesics, or both, or other active controls were considered regardless of whether single or multiple doses were administered.

An electronic search using Medline, Embase, BNI, CINAHL, CancerLit and the Cochrane Library was performed to identify the literature on topical opioids for painful cutaneous ulcers. Additional articles were identified from the reference lists of the retrieved papers, relevant reviews, and selected journals. Articles published up until December 2001 was included.

A detailed search strategy was developed for each electronic database searched based on the search strategy developed for Medline but revised appropriately for each database. The subject search used a combination of controlled vocabulary and free text terms based on the following search strategy for searching Medline:

1. opioid or opiate or narcotic or analgesic or morphine or diamorphine or oxycodone or hydromorphone or methadone or fentanyl
2. topical
3. sore or ulcer or wound
4. 1 and 2 and 3
5. Limit 4 to human and adults

The inclusion criteria for the systematic review were published studies containing primary data on the effectiveness of topical applications of opioids in the palliative care setting. To determine which regimens were the most effective and practical, evidence for each opioid was appraised individually. The primary outcome measure was pain relief and secondary outcome measures were time to onset of analgesia, duration of analgesia, and side effects, either local

or systemic. The data collection form also included information on wound aetiology, study size, and design to identify which wounds might be most suitable for topical treatment; evidence for the impact of associated necrosis, inflammation, infection, and exudate also was sought.

Data from all articles were extracted using a data collection form and the quality of individual studies was graded using levels of evidence recommended by the Centre for Evidence-Based Medicine and the Oxford Quality Score (Jadad et al. 1996) [Appendix 13.1].

2.2.2 Results of literature searches

Electronic and hand searching identified 216 studies [Figure 2.2]. Most papers were excluded on reading the abstract because they were beyond the scope of the review (e.g. acute or experimental pain, volunteer subjects or children), were duplicates, contained insufficient data (e.g. conference abstract), or were review articles.

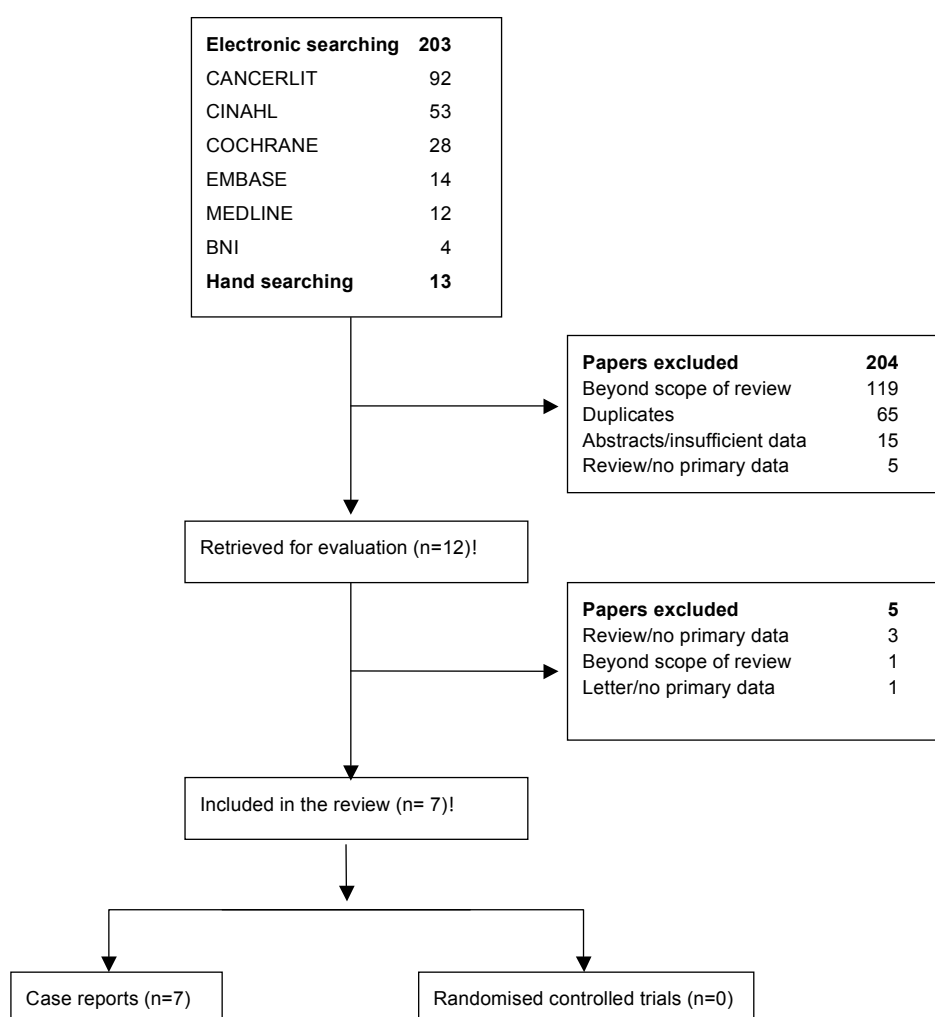
After reading the abstracts, 12 papers were identified of which seven (recruiting a total of 25 participants) met the inclusion criteria (Back & Finlay 1997; Krajnik & Zylicz 1997; Krajnik et al. 1999; Twillman et al. 1999; Flock et al. 2000; Grocott 2000; Paul 2000) [Table 2.2]. Importantly all were case reports with no published randomised clinical trials.

2.2.3 Summary of case reports and case series studying topical opioids on ulcers

Back & Finlay (1995) described three patients with painful skin ulcers; two with pressure ulcers and one with a malignant skin ulcer. All patients were receiving systemic opioids (a daily oral morphine equivalent dose range of 30-1500 mg) and were given 10 mg of diamorphine added to IntraSite gel applied topically to the ulcer once daily. All patients reported being more comfortable after the first diamorphine gel application, and the benefit appeared to last throughout the day. One patient with a questionable response had the diamorphine omitted

temporarily during which time she reported worse pain, and improved following the re-introduction of treatment. Two patients were treated for less than a week because of deterioration in their general condition; one patient continued the treatment for two months. No local adverse effects were noted.

Figure 2.2 Studies on topical opioids and painful ulcers identified in a systematic review of the literature (1965-2001)



Krajnik & Zylicz (1997) described a 76-year-old woman suffering from a non-Hodgkin's lymphoma who presented with a severe tense painful elevated cutaneous lesion in her scalp. Pain intensity was 5-7 on a 10-point numerical VAS, despite ibuprofen 400 mg taken three times daily. Unlike Back & Finlay (1995) who chose diamorphine, the authors used

Table 2.2 Studies identified in the systematic literature review

First Author	Design	Patients	Intervention	Outcome
Back 1995	Case reports	Three patients with painful ulcers (2 pressure, 1 malignant)	10mg diamorphine in 15ml IntraSite gel applied daily	Subjective pain relief reported
Krajnik 1997	Case report	One patient with painful malignant ulceration of scalp	4mg 0.08% morphine in hydrogel applied daily	Pain relief demonstrated by reduction in VAS score from 7/10 to 1/10. No adverse effects reported
Krajnik 1999	Case reports	Six patients with painful malignant and non-malignant lesions	Morphine hydrochloride/diamorphine hydrochloride/IntraSite 0.08-0.3% morphine gel applied twice or three times daily/ 10mg diamorphine	Pain relief and reduction in NRS reported in all patients
Twillman 1999	Case reports	Nine patients with painful malignant and non-malignant ulcers	0.1-0.15% morphine IntraSite gel applied twice daily or as required	7 reported substantial pain relief, 1 lesser response and 1 no response
Flock 2000	Case report	One patient with painful infected leg ulcers	0.1% diamorphine/0.75% metronidazole	Subjective pain relief described by patient
Grocott 2000	Case report	One patient with painful breast wound	10-20mg diamorphine in 15-30g IntraSite applied once or twice daily	Pain relief demonstrated by improvement in post treatment TELER score
Paul 2000	Case reports	Four patients with painful malignant and non-malignant ulcers	25-50mcg fentanyl mixed with KY jelly, Metrotop or Aquacell (depending on wound) applied daily	All patients reported reduced VAS scores. In two patients pain was abolished. No local or systemic adverse effects reported

0.08% morphine in hydrogel (4 g of gel, containing 3.2 mg of morphine), which was applied to 100 cm² of the scalp under occlusion. VAS score decreased from 7 to 1 within two hours, before increasing back to 6 some 25.5 hours after application. The gel was applied daily for seven days with continuing benefit and no adverse effects were noted. Treatment was discontinued when the patient developed other pain syndromes and she died seven days later

Krajnik et al. (1999) reported six cases where topically applied opioids were trialled. Three patients had cutaneous ulcers where either morphine or diamorphine was used probably reflecting the routine clinical practice of the respective authors. A 71-year-old woman with renal failure presented with painful necrotic leg ulcers approximately 480 cm². Pain intensity was rated 8 using a numerical rating scale (NRS). The wound was dressed with 30-50 ml 0.08% morphine gel (24-40 mg morphine) and analgesia occurred after 20 minutes and lasted for up to eight hours when the dressing was changed; NRS decreased to 4. After two weeks pain intensity increased and the morphine dose increased to 0.16% (48–80 mg morphine per dose) and the dressing changed twice daily. The wound improved with epithelialisation and decreased exudate and treatment continued for two months after which the wound deteriorated. A 69-year-old man with carcinoma of the larynx presented with a left supra-clavicular ulcer (over 6 cm²) and severe local pain described as severe burning and rated 9/10 on the NRS. Morphine gel (0.08%) was applied daily to the ulcerated area. In the first day pain decreased to 3 on the NRS and remained controlled (2 or less) for 4 weeks until his death. A 62-year-old female with carcinoma of the vulva presented with a fungating right painful groin lesion NRS rated 6. Diamorphine 10 mg mixed with IntraSite gel was applied into the wound cavity after which her pain score fell to 2. Dressings continued daily. After 10 days the wound appeared infected so the diamorphine was mixed with 1% silver sulphadiazine cream. Her pain remained under control for 4 weeks until she died, with pain scores consistently below 4. No adverse effects were reported in any of the cases.

Twillman et al. (1999) examined the use of either 0.1% or 0.15% weight-to-weight (w/w) concentration of morphine infused IntraSite gel in nine patients, eight of whom had open ulcers and one a swollen, inflamed bruised scrotum. Doses of morphine were applied directly to wounds, usually twice daily. Seven of the nine patients experienced substantial pain relief (reported either with verbal descriptors or using NRS), one patient experienced a lesser degree of analgesia and another patient without an open ulcer reported no pain relief; interestingly a patient with a subcutaneous infiltrate reported by Krajnik et al. (1999) but not described above experienced good pain relief despite no break in the skin. The use of morphine was well tolerated with no patients reporting systemic or local adverse effects; two patients were treated for over a year.

Flock et al. (2000) reported the case of an 82-year-old lady with metastatic ovarian cancer who had pain from multiple leg ulcers (stage I-III) of varying sizes. The patient was receiving oral analgesics that were initially ineffective and an increased dose lead to systemic adverse effects. Like Back & Finlay (1995), the authors chose to use diamorphine gel (0.1% concentration w/w equivalent to 1 mg diamorphine/1 mL IntraSite gel) that was applied topically to the ulcers every 48 hours. The patient was pain-free within one hour of application and remained so for 48 hours until the next dressing change. Subsequently some of the ulcers became infected and the IntraSite gel was switched to metronidazole gel (0.1% w/w equivalent to 1 mg diamorphine/1 mL metronidazole gel [0.75%]). The patient remained pain-free and the leg ulcers started to heal.

Grocott (2000) described a patient with an infiltrating carcinoma of the breast experiencing intense cutaneous stinging and irritation neither of which had improved with analgesics nor antihistamines. An area approximately 320 cm² was treated daily with 10 mg of diamorphine in 15 g IntraSite gel. Stinging and irritation were measured using a five point TELER indicators

scale for the dimensions of intensity and duration (where 0 is the deficit to be overcome and 4 and 5 are treatment goals). The doses of diamorphine and hydrogel, together with the frequency of application, were titrated over a period of eight days until symptom relief was achieved using 40 mg diamorphine divided between two applications; a morning diamorphine dose mixed in 30 g of hydrogel and, as reported by Flock (2000) an evening diamorphine dose mixed in 30 g of topical metronidazole for odour management.

Paul (2000) assessed four patients with painful malignant and non-malignant skin ulcers for pain relief, who then received gel containing fentanyl citrate (25 to 50 µg), applied topically once daily. VAS was recorded before and during the study period (range 5 -15 days). Systemic adverse effects, regular and rescue analgesia were recorded. All four patients reported a reduction in VAS, in two cases the pain was abolished and the need for oral rescue medication reduced. No systemic or local adverse effects were reported.

2.3 Discussion

The evidence for the efficacy of topical opioids identified from this systematic review is entirely based on case reports and limited by the small patient numbers. Furthermore, studies published in the literature are difficult to compare due to differences in methodologies. For example in the identified studies there were differences in the opioid used, the dose(s), the frequency of administration, the carrier vehicle, the evaluation of efficacy, safety and tolerability, the ulcer pathology and the duration of follow up. The case reports identified in the literature review may be confounded by selection and publication bias therefore the evidence provided would be considered weaker than that provided by case control studies and graded accordingly (Scottish Intercollegiate Guidelines Network 2008) [Appendix 13.2].

Research in a palliative care population is not without its challenges. Recruitment to studies can be difficult (Rinck et al. 1997; Kaasa et al. 2006) and attrition rate high during the study due to progressive illness or death (McCorkle et al. 1989; Addington-Hall et al. 1992). Although a number of measures are available for the assessment of pain (Caraceni et al. 2002), palliative care patients may find them difficult to use, particularly if they are weak, debilitated or have cognitive impairment (Cohen et al. 1995), furthermore pain may vary during the course of the day (Zeppetella et al. 2000; Zeppetella et al. 2001) and the type, size, stage of the wounds and frequency of dressing change may all affect efficacy as could the wound's underlying pathophysiology, the degree of inflammation and the perfusion of the tissue.

In most reports topical opioids improved the pain of cutaneous ulcers in patients whose pain had previously been refractory to, or had experienced adverse effects from, systemic opioids. Most studies demonstrated efficacy by reduction in pain scores and in some cases it was possible to reduce or even stop concomitant systemic analgesia. In many cases pain reduction occurred quickly. Farley (2011) has described unpublished work suggesting that in-vitro 50% of the morphine can be released from the gel in two hours and a steady state achieved after four hours providing a possible explanation for the relatively quick onset of action. However as the studies identified in the literature review were not blinded it is not possible to exclude a placebo effect.

The pain scores used in the identified studies include the NRS and VRS; some used both (Twillman et al. 1999) in others the description of numerical VAS makes the actual tool used unclear (Krajnik & Zylicz 1997). These measures have not been specifically validated for the assessment of wound pain. A five point TELER indicators scale for the dimensions of intensity and duration was reported in one study (Grocott 2000). TELER, an acronym for Treatment Evaluation by the LE Roux method provides a structure for documenting and reporting clinical

outcomes (Le Roux 1993), has been used for assessing malignant fungating wounds and the effectiveness of dressings (Grocott 1997). The tool was later updated and validated for use in symptom control as well as dressing performance (Grocott 2001). Other validated tools include the Toronto Symptom Assessment System for Wounds (Maida 2009).

An arbitrary starting dose of opioid was chosen in the identified case studies and as with intra-articular opioids, the effective dose of topically applied opioids appears to be relatively low (Kalso et al. 2002). Patients described analgesia despite a wide range of systemic opioid doses. In one report a predetermined dose was efficacious in three patients despite a 50-fold difference in their daily equivalent systemic morphine dose (Back & Finlay 1995). In most cases the starting dose appeared to be effective and in only a few cases was titration required. It is possible that patients responding less favourably may have benefited from an increased dose of opioid. Further work should establish the role of dose titration and the frequency of administration.

It is currently unknown which opioids are best suited to topical administration. Diamorphine, morphine and fentanyl were described in the identified studies [Table 2.2], each of which has different physicochemical properties that have important pharmacologic implications. Opioids are weak bases (pK_a for morphine = 8.0, diamorphine = 7.6, and fentanyl = 8.4). In solution, they dissociate into ionised and unionised fractions, the relative proportions depend upon the pH of the solvent and their pK_a . The unionised fraction is more diffusible than the ionised form; hence the local factors within the wound affecting pH may influence the efficacy of topically applied opioid.

Morphine was used in three studies. The major metabolites of morphine are morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) (McQuay et al. 1990). M3G does not

appear to contribute significantly to the analgesic effect of morphine, whereas the role of M6G remains uncertain; M6G administration to healthy volunteers has been shown to reduce pain initiated by a variety of noxious stimuli (Penson et al. 2000; Skarke et al. 2003; Romberg et al. 2004) although a lack of analgesic activity has also been reported (Lötsch et al. 1997). The discrepancies between studies may be, partly, due to the range of doses of M6G used in these studies, with low doses of M6G being insufficient to induce analgesic effects. Morphine has relatively low lipid solubility, a property that could support locally mediated analgesic effect following topical administration; bioavailability studies could help confirm this.

Diamorphine was used in three studies reported by centres in the United Kingdom (UK) (Back & Finlay 1995; Flock et al. 2000; Grocott 2000). Although sometimes preferred over morphine because of its greater solubility, the rationale for using it for topical administration is debatable. There is some evidence of a novel mu-receptor with which diamorphine, but not morphine, interact (Rossi et al. 1996). Diamorphine is generally considered to be a pro-drug, which in vivo is rapidly de-acetylated to an active metabolite, 6-mono-acetylmorphine (6-MAM) and then to morphine (Barrett et al. 1992). Furthermore diamorphine is more expensive than morphine and not commonly available outside the UK.

Fentanyl was reported in one case study (Paul 2000). It is a synthetic phenylpiperidine derivative approximately 100 times more potent and approximately 500 times more lipid soluble than morphine; consequently it is rapidly and extensively distributed in the body (Shafer & Varvel 1991). The physical characteristic of fentanyl may permit it to cross into the systemic circulation following topical administration to a cutaneous ulcer. Bioavailability studies would be required to confirm this however the doses used were small (approximately systemic equivalent to between 2.5 and 5 mg oral morphine) compared to usual background medication taken by this patient group.

A number of carriers were used for delivering the opioids of which the hydrogels were the most common. IntraSite gel, like other hydrogels, is designed for debridement of necrotic tissue and indicated for use in shallow and deep open wounds e.g. pressure sores, leg ulcers, surgical and malignant wounds, partial thickness burns, scalds, lacerations and grazes, and also for the treatment of granulating cavity wounds (Vernon 2000). The choice of wound dressing depends on a number of factors including the wound characteristics, the treatment goals, patient/caregivers capabilities and the available resources. The ideal dressing removes excess exudate and debris, maintains moisture at wound/dressing interface, permits evaporation of excess fluid, eliminates dead space, remains separate from wound bed, minimizes pain and is cost effective. IntraSite, therefore, may not be appropriate for all wounds and some parts of the body may be difficult to treat under occlusive dressings. Furthermore the application of gel is difficult to the open exudates wounds where much of the drug may be lost or diluted and flushed away by the wound fluid.

The potential advantage of topical opioid administration is providing pain relief whilst minimising systemic adverse effects. Indeed one study described a patient who developed adverse effects with oral opioids but not with topical opioids, the latter also providing superior pain control (Flock et al. 2000). Topically applied drugs, however, have the potential to produce local adverse effects, either through the drug and/or the carrier. Few local adverse effects have been described with topically administered opioids, although itching and skin irritation may be associated with the debriding action of the IntraSite gel. Some patients have used the treatment safely over the course of many months, suggesting that this is a safe route to administer opioids.

The ideal method of providing pain relief is healing of the ulcer but this is difficult in benign pressure ulcers and unlikely in malignant ulcers. There are data from animal studies suggesting that topical opioid administration may impair wound healing by inhibiting the peripheral release of neuropeptides (Rook & McCarsen 2007) and that the effects may be time-dependent (Rook et al. 2008). There was no evidence of delayed wound healing in the identified studies indeed some commented specifically on wound healing and the potential for palliative care to improve wound healing and the quality of life for patients and families living with chronic wounds is now being recognised (Schulz et al. 2002; Ferris et al. 2007).

There were no suggestions in the identified studies that patients exhibited signs of tolerance to topically administered opioid. Although the follow up periods in most studies were short, in two studies patients were followed up for two and 12 months respectively (Back & Finlay 1997; Twillman et al. 1999), and no signs of tolerance were reported. Although it is generally accepted in a palliative care setting that tolerance with systemic opioids is not a significant clinical problem (Collin et al. 1993; Grond et al. 1996), there are experimental data suggesting tolerance occurs with topical opioids, although this can be reversed by N-methyl D-aspartate receptor antagonists (Kolesnikov & Pasternak 1999).

Thus the evidence from this systematic review of previous studies on the use of topical opioids for painful ulcers is limited to only seven case studies recruiting a total of only 25 patients. Although these studies did suggest that topical opioid application might be a useful option in the management of painful skin ulcers there are many questions to address before this administration route can become routine medical practice. Such questions include which wounds are most likely to respond, which opioid, is preferred, at what dose, and at what dosing interval and which, if any, carrier should the opioid be mixed with.

Chapter 3: Aims of the Thesis

There is currently a limited amount of evidence regarding the utility of opioids administered topically for the management of painful cutaneous ulcers. A systematic review of the literature revealed a few small case studies but they employ different methodologies, opioids, doses, administration intervals and carrier vehicles, the evidence is of limited use. Furthermore there were differences in the evaluation of efficacy, safety and tolerability of the opioid, the ulcer pathology and the duration of follow up for patients studied. Therefore randomised controlled trials are required to assess the utility of topically applied opioids for the management of painful cutaneous ulcers

The potential benefits of delivering opioids peripherally by topical application include maximising opioid concentration at the site of pain, reducing plasma drug levels with potentially fewer adverse effects and fewer drug interactions. The presence of opioid receptors in the dorsal root ganglia, peripheral sensory nerves, lymphocytes, macrophages and mast cells in the presence of inflammation make this theoretically possible.

The null hypothesis is that morphine applied topically to painful cutaneous ulcers does not have an analgesic effect. The aims of the research project were to address the hypothesis in the following way:

- Describe the prevalence of the painful ulcers in a palliative care setting;
- Investigate the efficacy, safety and tolerability of topically applied morphine to painful ulcers;
- Determine the bioavailability of topically applied morphine;
- Determine the physical and microbiological stability of topically applied morphine;
- Make practical recommendations regarding the preparation, storage and use of opioids applied topically to painful cutaneous ulcers in a palliative care setting.

Chapter 4: Prevalence of painful cutaneous ulcers in patients admitted to a hospice

4.1 Introduction

A variety of wounds have been identified in patients with advanced illness including malignant, pressure ulcers, iatrogenic, traumatic, diabetic foot ulcers, venous leg ulcers, arterial ulcers/gangrene, infections/inflammatory lesions, and ostomy related (Maida et al. 2008). Most wounds tend to affect the sickest patients, namely, those with advanced illness and multiple co-morbid factors. Furthermore wounds may be associated with reduced life expectancy (Maida et al. 2009a).

Risk assessment tools are available that can help identify vulnerable patients and plan their care, particularly for the management of pressure ulcers (Pancorbo-Hidalgo et al. 2006). One such tool is the Waterlow Score Card [Appendix 13.3] developed for use in all aspects of health care (Kottner et al. 2009). One side of the Waterlow Score Card illustrates the risk assessment scoring system and the reverse side provides guidance on nursing care, types of preventative aids associated with the three levels of risk status, wound assessment and dressings. The Waterlow Score Card is a routine part of our own clinical practice as is an assessment of the patient's performance status, using the Eastern Co-operative Oncology Group classification (Oken et al. 1982) [Appendix 13.4], also considered to be a risk factor for wound development [Table 1.4].

Wounds are frequently associated with a number of clinical problems including pain, soreness and irritation from excoriated skin conditions, pruritus, odour, spontaneous bleeding and haemorrhage all of which would be considered in an assessment framework (Grocott 2001; Maida 2009). Other information that can have an impact on wound management includes age;

social and care environments; psychological perspectives; nutrition; medical diagnosis and associated disease processes; drug therapy and history of the wound, is usually also collected as part of the assessment process.

Pain is one of the symptoms that patients find particularly distressing (Franks et al. 1994; Charles 1995; Price & Harding 1996) and has a negative impact on their quality of life (Price & Harding 2004). Pain is a clinical challenge as it can vary from one patient to another and within the same patient (Krasner 1995). It may have nociceptive, neuropathic or mixed pathophysiological features. Pain may be constant, transient or both; transient pain may have specific precipitants such as dressing changes.

The management of pain in chronic wounds depends on comprehensive assessment, reporting and documenting patient experience of pain. Assessment should be based on six critical dimensions of the pain experience: location, duration, intensity, quality, onset and impact on activities of daily living (Price et al. 2007). Despite an increasing acknowledgement of the impact of wound pain the literature is limited, particularly in hospice patients.

4.2 Aims of case review

There are few data describing the characteristics of ulcers in patients admitted to hospices and thus the features of cutaneous ulcer-related pain that could then be addressed with topical application of opioid. The aim of this study was to describe the prevalence and characteristics of cutaneous ulcers in patients on admission to a hospice, with a particular emphasis on the presence and characteristics of the associated pain.

4.3 Methods

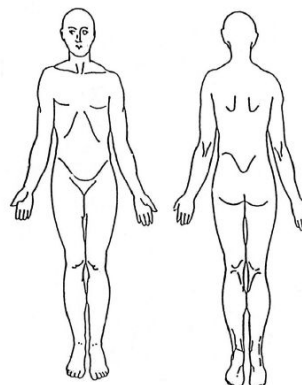
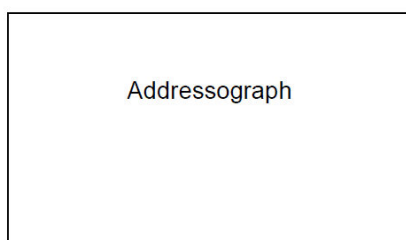
The clinical notes of all patients admitted to a hospice inpatient unit over a two-year period (April 2008 until March 2010) were retrospectively reviewed. The hospice has an eight bedded in patient unit that serves approximately 250 000 residents in West Essex and East Hertfordshire. Referrals included both cancer patients and patients with advanced non-cancer disorders and were received from community health care professionals (e.g. general practitioners, district nurses, and clinical nurse specialists), hospital health care professionals (e.g. doctors, ward nurses, and clinical nurse specialists) or other hospice, hospital or community specialist palliative care services.

The hospice uses multi-professional notes where entries are made by each member of the team. The notes have a number of sections dedicated to different aspects of the holistic assessment, including skin assessment and presence and characteristics of any identified ulcers. During the admission process the presence of ulcers is routinely assessed using the wound assessment chart [Figures 4.1 & 4.2]. When staff come into post they undertake mandatory training sessions, which includes training on the importance of the accurate completion of clinical notes, they then receive further training from a senior member of staff as their mentor. The clinical notes are periodically audited for Care Quality Commission purposes to ensure completeness and accuracy in all aspects of patient assessment and the results disseminated to staff as part of the hospice audit programme.

Patients admitted during the two year time period were identified by IT staff using the hospice patient database (iCare) and administration staff then identified the location of the clinical notes. I then retrieved and reviewed all the identified clinical notes in order to review and record the relevant data. The data were collected using a data extraction form designed for the case review [Figure 4.3]; additional information regarding the patients' analgesia was

Figure 4.1 Wound assessment chart within clinical record at St Clare Hospice describing each of the four ulcer stages

WOUND CARE ASSESSMENT CHART
Complete Assessment for each wound



DATE:

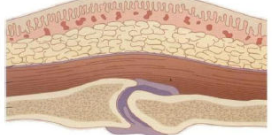
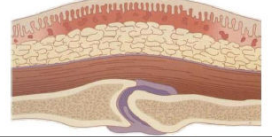
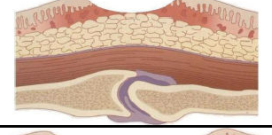
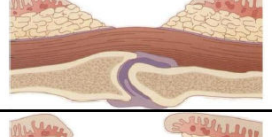
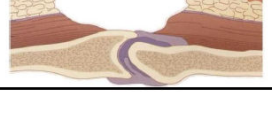
Stage	Nature of wound	Description of wound	Tick
0 	Blanching hyperaemia	Momentary light finger pressure onto the site of erythema following a prolonged period of pressure on the skin, causing the skin to blanch, indicating skin is intact	
1 	Non- blanchable erythema of intact skin	Discoloration of intact skin- blue/purple/black discoloration	
2 	Partial- thickness skin loss involving epidermis and /or dermis	Blister/abrasion/shallow ulcer, with/without undermining of adjacent tissue	
3 	Full- thickness skin loss involving damage of epidermis, dermis and subcutaneous tissue	Crater with/without undermining of adjacent tissue. Sinus. Necrotic tissue (hard or leathery black/brown tissue or softer yellow/cream/grey slough) which masks the true extent of tissue damage	
4 	Full-thickness skin loss with extensive destruction and necrosis to underlying tissue	Visible exposure of bone, tendon or capsule. Sinus assessed as extending to bone, tendon or capsule.	

Figure 4.2 Wound assessment collection form used as part of clinical record at St Clare Hospice

WOUND ASSESSMENT			
Type of wound		Diagram	
Aetiology (i.e malignant, pressure ulcer, arterial, venous, Surgical, Traumatic, Sinus/Fistula, Burn)			
Location			
Length of time ulcer/sore present			
General patient factors delaying healing (malnourished, diabetic, peripheral vascular disease, chronic infection, medication, incontinence, poor mobility)			
Allergies to wound care products			
Previous treatments tried			
Wound factors			
Healthy granulation (RED)			
Epithelialisation (PINK)			
Slough (YELLOW)			
Necrotic tissue (BLACK)			
Infected action taken-observation/ systematic treatment/local treatment/swabbed (Date			Wound care Plan
Exudate – amount increasing/decreasing / colour / consistency/ purulent/ haemoserous			
Odour – on dressing change / when dressing intact / present when entering room			
Wound dimensions length width depth			
Pain (site) Elsewhere (please specify using verbal rating score)			
Pain (frequency) Continuous/intermittent/only when dressing changed			
Condition of surrounding skin (fragile/reddened/dry/macerated/ oedematous/healthy/intact)			
Waterlow score			
Assessed by:			
Review Date & Complete New Assessment			

Reference Dealey C.(1999) The care of wounds: A guide for nurses 2nd Ed Blackwell: London

Figure 4.3 Ulcer prevalence survey: Data extraction form for patient number 27 identifying three painless grade 3 sacral pressure ulcers

Study number: 27

Patient number: [REDACTED]

Diagnosis: Ca prostate

Age: 80

Sex: Male ☒ Female ☐

ECOG performance status:

0	1	2	3	4
---	---	---	---	---

Nature of ulcer(s)

☒ Pressure ulcer (A, B, C)

☐ Malignant ulcer

☐ Other:

Classification [2]

Waterlow score [26]

A= 1 x 0.5 x 0.1 cm

B= 3 x 2 x 0.1 cm

C= 0.5 x 0.5 x 0.1 cm

Pain intensity

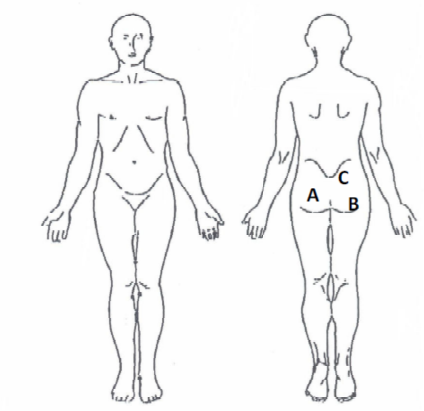
☒ No pain ☐ Mild ☐ Moderate ☐ Severe ☐ Excruciating

Analgesia

None

Efficacy:

Ineffective ☐ Partially effective ☐ Completely effective ☐



collected from the patient medication chart. To minimise omissions other sections of the clinical notes used during the admission process by either the nurses or the doctors were reviewed to cross check the information obtained from both the wound assessment and the medication charts. Missing data were noted during the collation process and identified during the analyses. Where results were analysed statistically non-parametric testing was used and a p value of > 0.05 was considered significant.

Formal ethical approval was not sought, but the survey was agreed by the hospice clinical governance working group and the hospice Caldicott Guardian, a senior clinician within the Hospice responsible for protecting the confidentiality of patient and service-user information and enabling appropriate information-sharing (Department of Health 2010).

4.4 Results

During the study period 323 patients were admitted, of whom 163 (51%) were females. The average age of all patients admitted was 70 years (range 25-96) and the most common diagnoses were primary cancers of the lung in 54 patients (17%), colon 38 (12%), breast 25 (8%) and pancreas 24 (7%). The notes of all 323 patients were examined. In two patients where the presence of ulcers was documented in the notes no wound assessment chart was completed. In other notes some aspects of the assessment were either absent, incomplete or illegible and are identified in the relevant section of the results.

In total, 125 patients (39% of all those surveyed) had cutaneous ulcers documented, the average age of this population was 72 years (range 26-93); 65 patients (52%) were male, and the most common diagnoses were primary cancers of the lung in 25 patients (18%), colon 11 (9%), and oesophagus 10 (8%); 4 patients (6%) had advanced non-cancer disease. The median (mean \pm SD) performance status of all patients surveyed was 2.0 (2.1 ± 1.1); for patients with

ulcers the value was 3.0 (3.1 ± 0.7) and those without ulcers 1.0 (1.4 ± 0.7). The median (mean \pm SD) Waterlow score of all patients surveyed was 17 (17.2 ± 5.2); for patients with ulcers the value was 22 (20.7 ± 4.8) and those without ulcers 15 (14.9 ± 4.1). Both performance status and Waterlow Scores were significantly higher in the patients presenting with ulcers compared to patients without ulcers ($z = -13.44$, $p < 0.001$ and $z = -8.86$, $p < 0.001$ respectively). The presence of co-morbidities was also higher in the ulcer group [Table 4.1], although this was not statistically significant ($\chi^2 = 5.9$, $p = 0.12$). Of the medications identified by the Waterlow Score as risk factor for pressure ulcers, corticosteroids and non-steroidal anti-inflammatories (NSAIDs) were prescribed to a greater proportion of patients presenting with ulcers compared to patients without ulcers; this was not statistically significant ($\chi^2 = 2.6$, $p = 0.3$).

A total of 221 cutaneous ulcers were identified. The majority of ulcers were caused by pressure 183 (83%); other causes were trauma 25 (11%), malignancy 7 (3%) and vascular 6 (3%). Most ulcer sites were sacral, 121 (55%); other sites included heel 28 (13%), elbow 24 (11%) and leg 20 (9%). The average ulcer classification score [see Table 1.4] was 2 and the average surface area was 8.2 cm^2 (range 1-112 cm^2); malignant ulcers were generally larger in size than the other three ulcer aetiologies [Table 4.2].

Not all assessments were fully completed, 39 ulcer classification data points were missing (pressure ulcers (32), trauma (6), vascular ulcers (1), malignant ulcers (1)), as were 30 pressure ulcers ulcer size data points. The missing data were removed from the denominator when calculating percentages [Table 4.2]

Table 4.1 Characteristics of patients admitted to a hospice according to whether or not they had cutaneous ulcers

	Patients without ulcers	Patients with ulcers
Number of patients	198	125
Male	95	65
Female	97	60
Average age (\pm SD)	68 (15)	72 (14)
Average Performance status (\pm SD)	1.4 (0.7)	3.1 (0.8)
Average Waterlow Score (\pm SD)	14.9 (4.1)	21.5 (4.8)
Patients with co-morbidities (%)*	30 (15)	70 (56)
• Diabetes	15 (8)	45 (36)
• Peripheral vascular disease	12 (8)	19 (15)
• Chronic infection	5 (3)	4 (3)
• Incontinence	3 (2)	14 (11)
Prescribed medication		
• Corticosteroid prescription	63 (32)	78 (62)
• Cytotoxics	5 (3)	2 (2)
• NSAIDs	29 (15)	43 (34)

* Some patients presented with more than one co-morbidity

Table 4.2 Duration and physical characteristics of ulcers identified in patients admitted to a hospice

Ulcer aetiology	Pressure	Trauma	Vascular	Tumour
Number of ulcers	183	25	7	6
Length of time (weeks) (\pm SD)	2.4 (1.4)	1 (0.3)	4.4 (2.3)	8.7 (3.9)
Mean ulcer grade score (\pm SD)	2.1 (1)*	1.4 (0.5)*	2 (0.8)*	2.3(1.5)*
Mean ulcer area (cm ²) (\pm SD)	7.4(6.6)*	2.4(3.1)	10(6.9)	51(34)
Ulcer appearance (%)				
• Healthy	11(6)	5 (20)	1(14)	0
• Epithelialisation	76 (42)	12(48)	0	0
• Slough	51(28)	5(20)	2(29)	4(67)
• Necrotic	45 (25)	3(12)	4(57)	2(33)
Number of painful ulcers (%)	126(69)	11(44)	6(80)	4(67)

* Values with missing data points

Of the 221 cutaneous ulcers identified, 147 (in 83 patients) were associated with pain [Figure 4.4]. Most painful ulcers, 126 (86%) were pressure sores, 11 (8%) were related to trauma, 6 (4%) to tumour and 4 (3%) were vascular. There was some variation in the temporal features

of the pain associated with cutaneous ulcers, 116 ulcers (79%) were described by patients as having a background pain, 76 (52%) were associated with transient pain and 45 (31%) were associated with both background and transient pain. Twenty four patients were able to identify factors precipitating transient pain namely, dressing changes [13 patients (8%)], pressure [6 (3%)] and movement [5 (3%)]. Of the 147 painful ulcers, 125 (85%) were described as either severe or excruciatingly painful; transient pain was usually more severe than background pain [Figure 4.5].

Thirty seven patients presented with a total of 56 painless ulcers (including two patients with spinal cord compression where the resulting sensory deficit may have masked any pain resulting from the ulcer); eight patients had a mixture of painful (10) and painless (9) ulcers. Five patients (presenting with nine ulcers) were too unwell to report whether or not their ulcers were painful.

Of the 83 patients with painful ulcers, seven (8%) were prescribed analgesia specifically for the pain namely oral paracetamol as required (1 patient), oral paracetamol prescribed regularly (1), oral morphine as required (4) and oral oxycodone as required (1). Three patients using morphine and the one using oxycodone described their efficacy as partially effective, the remainder found analgesia ineffective.

Figure 4.4 Patients admitted to a hospice inpatient with and without cutaneous ulcers, and whether or not the identified ulcers were associated with pain

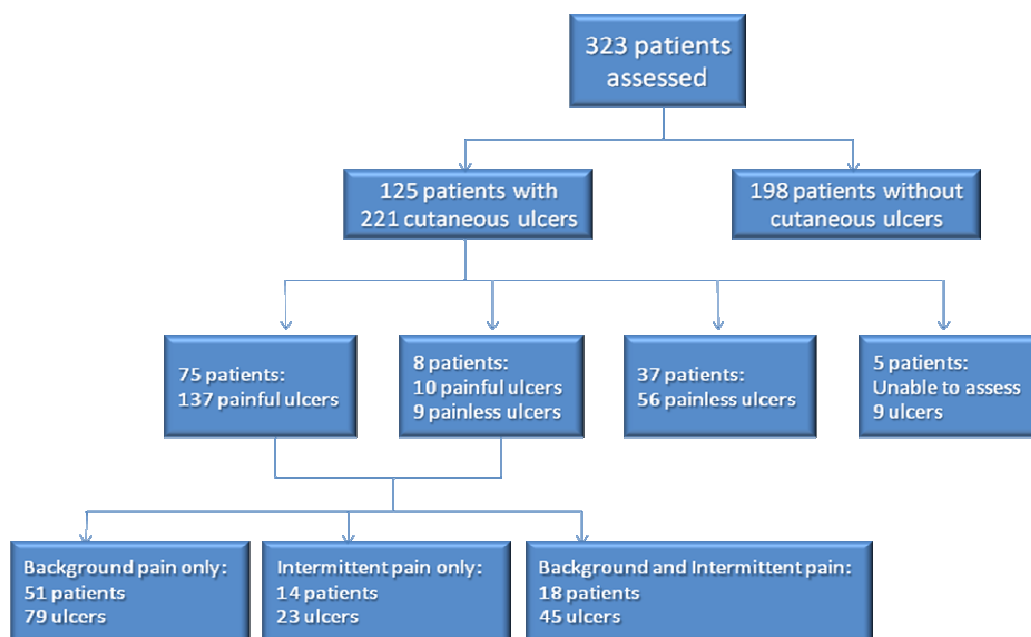
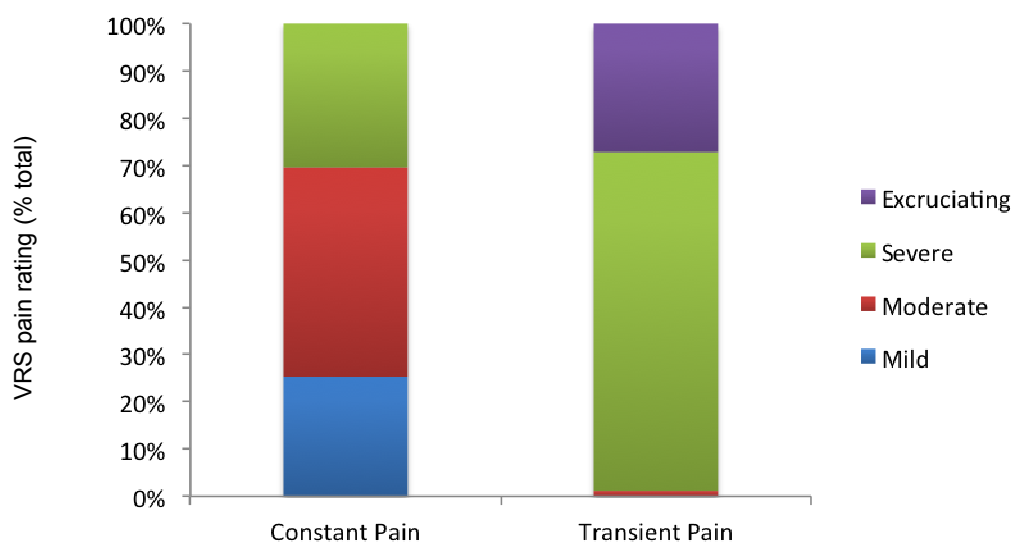


Figure 4.5 Verbal rating score (VRS) of constant (n = 99) and transient (n = 85) pain severity from cutaneous ulcers reported by patients on admission to a hospice



4.5 Discussion

Chronic wounds usually occur as a result of local disorders of nutrition in the skin, caused by venous, arterial or neuropathic vascular damage or prolonged local pressure or radiation, they may also be a symptom of a systemic disease such as infection or malignancy. Almost 40% of patients admitted to the hospice had cutaneous ulcers, most of which were grade II pressure sores (i.e. partial thickness skin loss or damage involving dermis or epidermis) and their distribution was in keeping with the expected pattern namely in areas of bony prominence [Figure 1.3]. The average performance status of patients surveyed was 3 (i.e. capable of only limited self-care; confined to bed or chair for 50% or more of waking hours) and this together with a Waterlow score of 17 emphasises that patients admitted to the hospice were at a high risk of developing pressure sores.

Most ulcers were painful and in the majority the severity was rated as either severe or excruciating. The variability of wound pain has been described elsewhere and three types identified: cyclic (periodic discomfort), non cyclic (single incident) and chronic (persistent discomfort) (Krasner 1995); the patients surveyed reported all three pain types. In order to accurately determine the patient's type of pain a comprehensive assessment is required that addresses not only background pain but also the transient exacerbations of pain that were more severe than background pain. The exacerbations of pain that occur in the presence of controlled background pain are commonly referred to as breakthrough pain (Davies et al. 2009). Currently there are no validated clinical tools for the assessment of breakthrough pain and tools such as the Brief Pain Inventory that assess worst pain, least pain and average pain may be helpful (Cleeland 1993). A systematic review identified the McGill Pain Questionnaire, the Faces pain scales, and the visual analogue scale as potential tools (Pieper et al. 2009) however they do not capture all the elements of cancer pain experienced by the patient (Gorecki 2011).

The prevalence of malignant ulcers in this survey was 3% and lower than seen in other studies where a prevalence rate of approximately 15% has been reported (Maida et al. 2008b; Maida et al. 2009). Malignant wounds have been reported to be most prevalent in patients with breast cancer where prevalence rates between 30 and 40% have been reported (Lookingbill et al. 1993; Wilkes et al. 2001; Maida et al. 2009), although lower prevalence has been described (Stotter et al. 1991). Perhaps an explanation of the lower number of ulcers in this survey was that the number of patients presenting with breast cancer was only 8% of the survey sample.

Malignant wounds may be classified into four principal classes: nodules and induration, fungating, malignant ulcers, and mixed (Maida et al. 2008a; Schultz 2005), in this survey two patients had fungating wounds and four had malignant ulcers. Pain is only one symptom complicating malignant wounds. For example Maida et al. (2009), found that in a series of patients with malignant wounds, most were associated with mass effect (i.e. reduced mobility of limbs and spine and difficulties with clothing experienced with fungating wounds), aesthetic distress, exudation, odour, pruritus, bleeding, and crusting. The assessment of pain is therefore only one element of the wound assessment that requires management, although some treatment modalities considered for other symptoms (e.g. radiotherapy and chemotherapy) may also improve pain.

Pain from pressure sores has been reported to interfere with patients' ability to undertake daily activities and particular movements, engage in and enjoy socialising; leads to anxiety, fatigue, decreased appetite; and contributes to emotional distress (Gorecki et al. 2009).

Although many of the patients surveyed were experiencing pain from their ulcer, relatively few had been prescribed analgesia prior to admission. Despite the availability of several guidelines for cancer pain management (Jacox et al. 1994; WHO 1996; Hanks et al. 2001; Cohen et al. 2003; Scottish Intercollegiate Guidelines Network 2008), it is clear that many of the patients

surveyed did not have adequate pain relief. A systematic literature review of studies using the Pain Management Index (PMI) as a tool linking pain severity to intensity/strength of the analgesic therapy identified 26 studies within which 43% of cancer patients have a negative PMI score suggesting nearly one in two patients were undertreated (Deandrea et al. 2008).

The reasons for under treatment of pain in cancer patients are varied and can relate to either the patient (e.g. wanting to be a “good” patient, reluctant to distract the clinician from treating the primary disease, may not want to recognise that their disease is progressing, fears of becoming addicted or tolerant to analgesics) or health care professionals (inadequate knowledge, poor pain assessment, anxiety about regulation of controlled substances, concerns about the adverse effects of analgesics and fear of patients becoming addicted or tolerant to analgesics) (Ward et al. 1993; Von Roenn et al. 1993), any of which may have played a role in the patients surveyed.

The first documentation of wound care can be found in an ancient Egyptian papyrus of 1600 BC, with a description of the removal of devitalised skin and pus following war injuries (Majuno 1975). Although the literature on chronic wound management has evolved over the years the increased knowledge has not translated into everyday clinical practice. Despite being a key clinical indicator, wound pain has been traditionally neglected by health care providers with a lack of documentation and treatment. Woo et al. (2008) produced a set of 18 statements supported by a literature review that identified 170 articles that met the criteria of temporary and persistent wound pain and agreed by a group of experts [Table 4.3]. However producing a statement is a relatively simple process; the challenge is its implementation.

There may be some confusion of clinical roles when managing patients with chronic wounds (Bennett & Moody 1995). Doctors may feel their role is to focus specifically on the underlying disease; in the case of malignant wounds there may be a positive impact on pain whereas for pressure ulcers this is unlikely. Moreover doctors may consider the management of ulcers to be a specific nursing role, despite this the nurse will require the support and advice from doctors for prescribing dressings and analgesics. Ideally a group of clinicians, often multi-professional, with knowledge and expertise of wound care management should be clinically responsible for patients. Perhaps greater availability and use of tissue viability clinical nurse specialists may help improve the care of patients with chronic wounds (Flanagan 2008).

Table 4.3 Statements for the assessment and management of persistent (chronic) and total wound pain (Woo et al. 2008)

1. Assume all chronic wounds are painful until the patient indicates otherwise
 - a. Assess and study chronic wound pain on a regular basis
 - b. The patient should be assessed with the same standardised tool at every assessment
 2. Wound pain occurs with activities of daily living, not only at dressing change
 3. Discuss with patients and caregivers the options for wound pain management based on assessment results
 4. Consider non pharmacological and pharmacological wound pain management options
 5. Increased wound pain requires reassessment of underlying conditions or aetiologies for treatable causes
 - a. Increased wound pain may be an important clinical symptom of infection or inflammation
 6. Treat the cause and treat the wound pain with the patient's active participation
 7. Wound pain often adversely affects activities of daily living and patient well-being; effective management may lead to improvement
 8. Prevent and/or minimise anticipatory and procedural wound pain by using appropriate pain management techniques
 9. An on-going therapeutic relationship between the inter-professional team and the patient is essential for wound pain management
 10. Communicate, educate and implement the wound pain management plan verbally and with documentation to the patients, caregivers and the inter-professional team
-

Case studies are descriptive studies usually conducted when little is known about a problem or little is known about the occurrence of a known problem (Costantini & Higginson 2007). Case studies, such as this retrospective case note review have the advantage of being practical and feasible to plan, they are inexpensive, have the ability to use existing records, allow study of rare occurrences, and are easier to assess conditions where there is a long latency between and exposure and disease. Case studies also have limitations as they rely on accuracy of written record or recall of individuals, there may be important data may not be available, and bias is difficult to control as there is no blinding or randomisation (Hess 2004), referral bias may also be an issue so that the patients surveyed represent those with more complicated disease and the findings may be unrepresentative of the population as a whole, as the survey does not contain control groups, Furthermore the survey does not take into account other methods of managing painful wounds such as dressings, special mattresses or other equipment. Hence this case note review is best suited at generating hypotheses that can then tested prospectively by other methods and not for establishing cause and effect.

4.6 Summary

This case note review showed that cutaneous ulcers were a common problem in patients admitted to our hospice. Most cutaneous ulcers were pressure ulcers that result from the poor general state of health of the patients admitted. The majority of ulcers identified in this survey were painful and different patterns of pain were described. Very few patients were prescribed analgesia and in those that were, most derived little benefit.

Chapter 5: Efficacy, safety, and tolerability of opioids applied topically to painful cutaneous ulcers

5.1 Introduction

Cutaneous ulcers have a significant impact on patients in a palliative care setting and their management is often inadequate. Cutaneous ulcers may have a variety of causes including trauma, pressure, circulatory problems and malignancy; furthermore skin ulcers may become infected adding to the management challenge. Pain is one of the symptoms associated with cutaneous ulcers, however the evidence presented in Chapter 4 suggests that pain is poorly managed. Many patients are not prescribed analgesia and in the minority of patients that are it is either ineffective or results in systemic adverse effects.

Topical application of drugs provides a direct, localised effect on a specific area of the skin. Topical medications can be delivered via a variety of formulations including creams, ointments, gels and lotions. Analgesics such as NSAIDs have been formulated for topical use and systematic reviews comparing trial of topical with oral NSAIDs have concluded they were equally efficacious (Moore et al. 1996). Importantly, topical application of NSAIDs is not associated with serious adverse effects, and therefore provides an effective method of pain relief without the gastrointestinal effects seen with the same drugs taken orally.

The premise that opioids exert a local analgesic effect is based on the fact that opioid receptors have been found on peripheral nerves and inflamed tissue, and peripheral opioid injections for local analgesia, such as intra-articular morphine after knee surgery, have been found to be effective in several trials (Kalso et al. 2002). Evidence from single case reports and case series suggests that topical opioids are beneficial in the management of pain associated with benign or malignant skin ulcers in palliative care patients (Chapter 2). Topical opioids can

be used as an adjunct to systemic analgesia and reduction or cessation of concomitant systemic analgesics may be possible.

5.2 Aims of efficacy studies

The aim of this study was to investigate the efficacy of topically applied morphine in hospice inpatients using a randomised, double blind, placebo controlled crossover study design. Two trials are reported a pilot study, to determine the feasibility of undertaking such study in a hospice inpatient population, and a subsequent larger study. Ethical approval for both studies was obtained from the local ethics committee [Appendix 13.5].

5.3 Pilot study: Methods

Hospice inpatients were eligible for the study if they had a painful cutaneous ulcer that was neither infected nor covered by necrotic tissue and was suitable for once daily treatment with IntraSite gel. Patients had to be capable of completing numerical rating score (NRS), and were receiving a stable analgesic regimen for at least 48 hours prior to recruitment. For the purpose of the study, if the patient had ulcers on more than one site, only one site was chosen for topical opioid treatment.

Following written informed consent and, using a table of random numbers, patients were randomly assigned to receive either morphine (1 mL morphine sulphate injection 10 mg/mL in 8 g IntraSite gel) or placebo (water for injection 1 mL in 8 g IntraSite gel). The person obtaining consent was blinded to the randomisation sequence. Treatment was applied once daily (in the morning), after which the ulcer was covered with a Tegaderm dressing. Patients were treated for two days followed by a two-day washout period, after which they were crossed over to the alternative treatment. During the six-day study period, no changes were permitted in regularly scheduled analgesia; rescue analgesia was available for the patient to use when required.

Patients were asked to assess the analgesic effects of each treatment arm by completing an 11-point NRS score (0 = no pain and 10 = unbearable pain) twice daily, the first score was at least two hours after the morning dressing, the second score in the afternoon/early evening. Patients and nursing staff also recorded any local or systemic adverse effects experienced or observed during the course of the study [see Appendix 13.6]. The average NRS scores for the treatment arms for each patient were compared using a Wilcoxon rank test for non-parametric data. A P value less than 0.05 was considered to indicate statistical significance.

5.4 Results

Five patients with advanced malignant disease were recruited for the pilot study and randomised to order of treatment. All patients had painful sacral pressure sores ranging in surface area from 4.5 to 14 cm². Most patients were already using a regularly scheduled opioid for analgesia; one patient was using an oral NSAID. Patients rated their background pain in the 24 hours immediately prior to starting the study as mild (2 patients), moderate (2) and severe (1) [Table 5.1].

Table 5.1 Characteristics of patients recruited to a pilot double blind placebo controlled cross over study

Patient	1	2	3	4	5
Sex	Male	Female	Male	Female	Male
Age	80	87	78	62	81
Primary cancer	Lung	Pancreas	Prostate	Lung	Mesothelioma
Ulcer area (cm ²)	4.5	8	7.5	8.25	14
Stirling score	2	2.4	2.3	2.3	2.4
Scheduled analgesia	Oramorph 2.5mg 4 hourly	MST Continus 20mg 12 hourly	Diclofenac 50 mg 8 hourly	MST Continus 30mg 12 hourly	MST Continus 30mg 12 hourly
Ulcer pain intensity*	Moderate	Mild	Mild	Moderate	Severe

* Average pain intensity over 24 hours prior to starting the trial

Table 5.2 Pilot double blind placebo controlled cross over study: Patient numerical rating score (NRS) following morphine* and placebo administered topically to painful ulcers and NRS during washout period

Patient	1	2	3	4	5
<i>Placebo NRS scores</i>					
Day 1 morning	2	1	3.5	5	8
Day 1 afternoon	5	5	2.5	8	8
Day 2 morning	2	5	3.5	0	7
Day 2 afternoon	8	7	3.7	7	2.5
Mean	4.25	4.50	3.30	5.0	6.38
<i>Washout NRS scores</i>					
Day 1 morning	6	0	1	6	7
Day 1 afternoon	6	5	1	2	4
Day 2 morning	5	4	4.5	5	4
Day 2 afternoon	4	8	4	5	5
Mean	5.25	4.25	2.63	4.50	5.00
<i>Morphine NRS scores</i>					
Day 1 morning	2	2	2.5	4	1
Day 1 afternoon	0	0	1	8	2
Day 2 morning	0	1	0.25	0	1
Day 2 afternoon	0	2	0	1	1.5
Mean	0.50	1.25	0.94	3.25	1.38

*Patients #1 & 4 received placebo first, patients #2, 3 and 5 received morphine first.

Patients completed NRS scores twice daily, in the morning and afternoon during each treatment arm and the washout period [Table 5.2]. One patient appeared to have difficulty highlighting specific numbers on the NRS with seven of the 12 scores were marked between two numbers [Appendix 13.6]. In these instances the value was determined by measuring the distance from the lower score and expressing the value as a percentage of the distance in between the two scores.

The NRS scores were highly variable particularly for the placebo arm and the washout period. The median (mean \pm SD) NRS score for all patients during placebo, washout and morphine was 5 (4.67 ± 2.55), 4.75 (4.33 ± 2.03) and 1 (1.46 ± 1.87) respectively. There was a statistically significant difference between the NRS scores during the two treatment arms ($p < 0.01$) and the scores during opioid treatment and the washout period ($p < 0.01$). There was no difference between the placebo treatment arm and the washout period ($p > 0.05$).

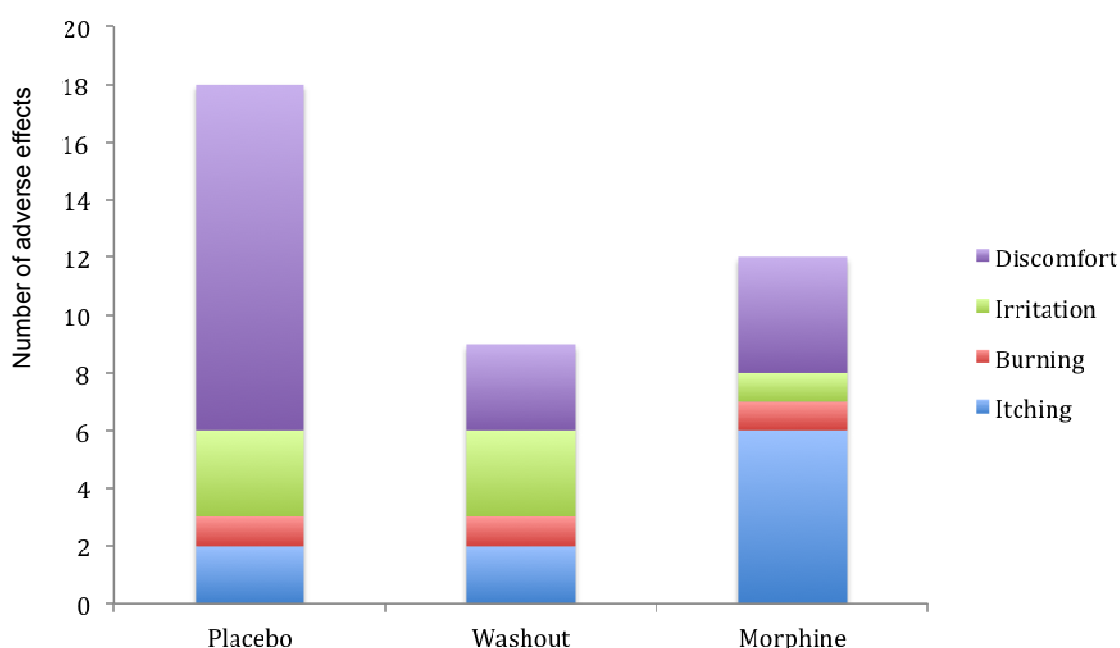
Some patients appeared to respond better than others. Patients 1 and 3, for example, were pain-free on day 2 of morphine treatment, which may imply that the treatment is effective but did not have an immediate onset. Patient 5, however, appeared to benefit from placebo, as NRS scores fell from 8 to 2.5 in the two-day period, whereas the NRS scores during morphine, although low, showed no improvement.

During the trial period patients had their usual rescue medication to take, as they required. There was no difference in the patients' use of rescue medication throughout the trial; the mean (\pm SD) number of daily rescue doses taken was 2.3 (1.4) during placebo, 2.0 (1.6) during morphine treatment and 2.1 (1.2) during the washout period ($p > 0.1$).

Systemic adverse effects were monitored during the study. The number of patient reports (n), mean NRS \pm SD for nausea during placebo phase was n = 8, 0.78 ± 1.88 , washout n = 7, 0.79 ± 1.13 and during morphine n = 6, 0.5 ± 0.83 and for drowsiness during placebo phase was n = 13, 3.35 ± 3.04 , washout n = 6, 2.75 ± 2.82 and during morphine n = 9, 2.71 ± 2.70 . Although drowsiness occurred more frequently than nausea there was no difference in each of the symptoms during the three phases of the study ($p > 0.1$).

Most patients reported local symptoms associated with the ulcer. Patients 2, 4, and 5 reported localised discomfort while treated with placebo but not with morphine, and patients 1 and 3 noted itching, burning, and discomfort during treatment with both morphine and placebo. None of the local adverse effects appeared specifically attributable to morphine. Patients reported discomfort, other than pain, on 19 occasions and most commonly during placebo treatment days [Figure 5.1]. Thirty seven symptoms were reported and these occurred more frequently during placebo treatment when compared to morphine ($\chi^2 = 7.13$, $p = 0.07$); no differences were found between morphine treatment and washout days ($\chi^2 = 2.8$, $p = 0.42$) and placebo treatment and washout days ($\chi^2 = 3.87$, $p = 0.28$).

Figure 5.1 Local adverse effects reported by the five patients during the placebo, washout and morphine phases of the pilot study



Patients were asked at the end of the six treatment days which days they experienced the least amount of pain. Three patients selected the days they were treated with morphine and two reported no difference across the six days treatment.

5.5 Discussion

This pilot study found that patients with painful pressure sores found morphine to be a more effective analgesic than placebo. Furthermore, morphine was generally well tolerated by patients, and although local reactions were described during the study, these were mild and probably not related to morphine. These findings are consistent with the positive results of previous case studies.

Some patients appeared to respond better than others. Patients 1 and 3, for example, were pain-free on day 2 of morphine treatment, which may imply that the treatment is effective but did not have an immediate onset. Patient 5, however, appeared to benefit from placebo, as NRS scores fell from 8 to 2.5 in the 2-day period, whereas the NRS scores during morphine, although low, showed no improvement.

NRS scores varied considerably during the course of the pilot study. Patient 3, for example, appeared pain-free in the morning of day 2 while on placebo, yet that afternoon was in severe pain. This is not totally unexpected as cancer pain intensity can vary during the course of the day (Zeppetella et al. 2000). Such variations may complicate assessment and measuring multiple NRS scores (worst pain, least pain, and average pain over the preceding 24 hours (Cleeland et al. 1994) may be necessary. The potential variation in pain intensity also underlines the potential value of a local treatment; as if pain spontaneously subsides systemic adverse effects would not be problematic.

The data from the cancer pain literature suggest that NRS is an appropriate measure based on its intrinsic properties (Cepeda et al. 2003). The NRS is an example of a uni-dimensional pain measurement tool that is well validated in the cancer population and is also commonly used to measure pain relief (Caraceni et al. 2002; Hjermstad et al. 2011). Furthermore when compared

to the VAS, the NRS has a significantly higher discriminatory capability to distinguishing between background and pain exacerbations (Brunelli et al. 2010), which might be applicable for patients with pressure pain than occurs or worsens spontaneously, on movement or during dressing changes. However frail patient, such as those entered into the study, may fail to understand or see how to mark the intended number. Patient 3 for example appeared to mark a spot in between two numbers on seven of the 12 assessments, whereas patient 5 did it twice. This can cause some confusion and for the purpose of the pilot study the score was taken by measuring at what point the patient had marked between the two numbers; a verbal rating documented by staff may have proved more accurate (Bijur et al. 2003).

None of the patients surveyed reported systemic adverse effects specifically related to morphine, including patient 3, who was opioid-naïve. This finding could support a local mode of action. A pharmacokinetic evaluation measuring serum morphine and its metabolites following topical administration would be required to support a local mode of action. It was not possible to run this alongside the pilot study as most patient were taking oral opioids which would have made it difficult to distinguish the metabolites from systemic opioid and from opioid topically to the wound.

Limited conclusions can be drawn from this pilot study, not only because of the small number of patients but also because a single dose was used. It is possible that patients responding less favourably may benefit from an increased dose of morphine. A dose titration study would be necessary to explore this further. Interestingly, patient 5 had the largest ulcer (three times larger than patient 1), and although one could assume that larger ulcers require higher analgesic doses, the actual situation is likely to be more complex and requires specific investigation. In order to explore these findings further a larger trial was undertaken.

5.6 Randomised double blind placebo controlled cross over study

The pilot study suggested that patients with painful cutaneous ulcers found morphine applied topically to the ulcer was a more effective analgesic than placebo. These findings were consistent with the positive results from previous case reports. A larger study was therefore undertaken using similar methodology

5.6.1 Randomised double blind placebo controlled cross over study: Methods

This was a single centre randomised, double-blind, placebo-controlled crossover study comparing morphine sulphate and IntraSite verses placebo (water for injection) and IntraSite applied topically to painful skin ulcers undertaken in a 63-bedded UK hospice inpatient unit.

Patients were eligible for the study if they had been an inpatient at the hospice for at least 48 hours; were 18 or more years old; were able to give voluntary informed written consent; were able to complete a pain score diary; they had an expected prognosis of greater than two weeks; were on an analgesic regime that has been stable for at least 48 hours; and that the ulcer was painful in the area of skin ulceration, suitable for once daily treatment with IntraSite, had any infection treated before entering the study and any layers of necrotic tissue removed before the study. If the patient has ulcers on more than one site, only one site was chosen and that site identified at the first assessment.

Patients were ineligible for the study if they had a history of substance abuse; were confused or had a reduced level of consciousness, which in the opinion of the investigator could preclude participation in the trial; had a concomitant psychiatric disorder; there was a history of serious adverse events to strong opioid drugs in the past; there was a history of serious adverse events to IntraSite in the past; the maximum diameter of the painful ulcerated area greater than 20 cm (to exclude the potential of systemic absorption); the patient had

participated in any other clinical trial or research which would interfere with the current study; it was the opinion of ward staff attempts to recruit the patient into the study would cause undue distress to them or their carers; the patient was pregnant or breast feeding; there was clinically significant renal failure.

For subjects satisfying the inclusion criteria and after giving written informed consent, a pre-trial assessment will be completed which included, identifying the ulcer site; tracing the ulcer (this was repeated at the end of the study to determine whether or not there had been a change in the ulcer size); determining the ulcer's aetiology; classification of the ulcer using the Stirling method; determining the Waterlow score; determining the patient's ECOG performance status.

Following assessment patients were randomly assigned, using a table of random numbers, to receive either morphine (1 mL morphine sulphate injection 10 mg/mL in 8 g IntraSite gel) or placebo (water for injection 1 mL in 8g IntraSite gel) topically to their ulcer. The ulcer was first exposed by removing the previous dressing and then thoroughly cleaned before either saline or morphine was applied to it. Following the procedure the ulcer was covered with a Tegaderm dressing. Patients were treated for two consecutive days with one treatment followed by a two-day washout period after which they were crossed over to the alternative treatment. During the washout period the ulcer was cleaned in the same way but only IntraSite gel was directly applied to the ulcer. During the six-day study period, no changes were permitted in regularly scheduled analgesia, but their usual rescue analgesia remained available.

During the assessment patients were asked to verbally rate the pain from the ulcer over the previous 24 hours using an 11-point NRS (0 = no pain, 10 = worst pain possible) at start of the study (baseline) and then every day during the six-day study. Nurses were also asked to

identify whether the ulcer was painful whilst being dressed. Patients were asked to record adverse effects throughout the study by completing a NRS for common systemic adverse effects (or any others they experienced) and asked about local reactions. Nurses were also asked to identify local and systemic adverse effects. Patients were withdrawn from the study if a serious adverse experience occurred; the staff considered, for safety reasons, in the best interest of the subject that he/she be withdrawn; the patient withdrew his or her consent. The date and the reason for discontinuation were documented.

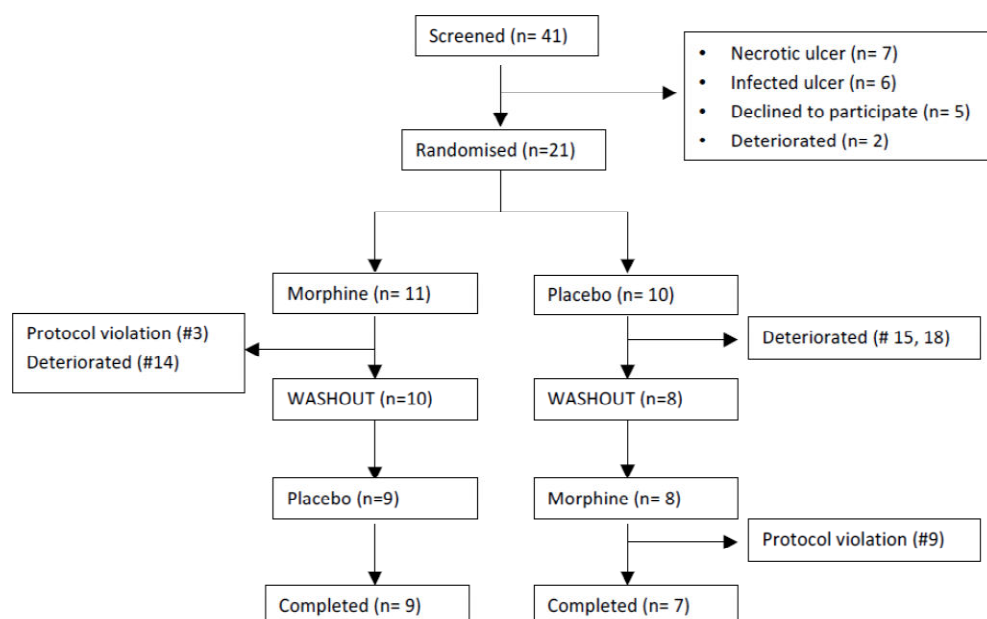
Primary outcome was the change from baseline in average pain intensity for each of the two treatment periods. Secondary outcome measures included patient preference at the end of the trial for either the morphine or placebo treatment days and use of rescue medication during the different treatment periods. Sample size was not calculated beforehand, as there was insufficient data upon which to base the calculation, however the aim was to recruit fifty patients but the study terminated early for administrative reasons. In the analysis, patients withdrawing from the study following randomisation were included in an 'intention-to-treat' (ITT) analysis; 'per protocol' (PP) patient outcomes were also included as a comparison. Statistical analysis was made using two-tailed non-parametric paired or unpaired test as appropriate. A P value less than 0.05 was considered to indicate statistical significance.

5.6.2 Results

A total of 41 patients were screened between March 2002 and April 2003, of whom 21 were enrolled into the study and randomised to order of treatment [Figure 5.2]. The median (mean \pm SD) age of enrolled patients was 78 (77 ± 7), the median (mean \pm SD) ECOG and Waterlow scores were 3 (3.24 ± 0.54) and 25 (25 ± 5) respectively; most were male [Table 5.3]. Most patients presented with pressure ulcers. The median (mean \pm SD) for the ulcer surface area was 16.5 (10.2 ± 14) and the ulcer grade was 2.3 (2.6 ± 0.5). All but two patients were taking

opioids as regularly scheduled medication. The median (mean \pm SD) daily morphine dose equivalent was 60mg (76.4 \pm 57.5). Five patients did not complete the study (deterioration (3), protocol violation (2)) but are included in the intention to treat analysis.

Figure 5.2 Study Disposition (CONSORT Diagram)



A total of 109 assessments from a possible total of 126 were made during the course of the study. Of the assessments made, 37 (34%) were during morphine treatment days, 37 (34%) were during placebo treatment and 35 (32%) were during the washout phase.

The NRS score for patients at pre-trial (baseline), during morphine, washout and placebo phases are shown in Table 5.4. All 21 patients randomised to order of treatment are included in the ITT analysis; the data for 16 patients who completed the study are also shown. The median, upper and lower quartiles, minimum and maximum NRS at baseline and during morphine, washout and placebo treatment periods for the ITT population is shown in Figure 5.3.

Table 5.3 Characteristics of patients recruited and randomised to the double blind placebo controlled cross over study

Patient	Sex	Age	ECOG	Waterlow score	Primary Cancer	24 hr oral morphine equivalent (mg)	Ulcer characteristics		
							Size (cm ²)	Aetiology	Classification
1	Female	72	3	20	Lung	25	6	Pressure	2.2
2	Male	78	3	27	Prostate	60	8.9	Pressure	2.3
3	Male	75	3	21	Colon	120	20	Pressure	3.1
4	Male	71	4	23	Lung	40	5.2	Pressure	2.3
5	Female	75	3	33	Oesophagus	Nil	12.5	Pressure	3.1
6	Male	70	4	34	Lung	160	14	Pressure	3.2
7	Female	85	2	27	Lung	240	38	Pressure	2.3
8	Male	89	3	22	Stomach	80	5	Pressure	2.2
9	Male	81	3	25	Lung	90	15	Pressure	2.3
10	Female	92	4	18	Lung	60	14	Pressure	2.2
11	Male	79	3	22	Mesothelioma	20	22.4	Pressure	2.3
12	Male	82	3	19	Lung	Nil	9	Pressure	2.2
13	Male	71	3	26	Colon	20	15	Malignant	2.3
14	Male	83	4	26	Pancreas	120	30	Pressure	3.2
15	Female	79	4	27	Breast	80	32	Pressure	2.3

Table 5.3 (Continued) Characteristics of patients recruited and randomised to the double blind placebo controlled cross over study									
Patient	Sex	Age	ECOG	Waterlow score	Primary Cancer	24 hr oral morphine equivalent (mg)	Ulcer characteristics		
							Size (cm ²)	Aetiology	Classification
16	Female	80	3	29	Mesothelioma	120	8	Pressure	3.1
17	Male	65	3	25	Bladder	40	30	Malignant	3.2
18	Female	74	4	31	Breast	120	26	Malignant	3.2
19	Female	75	3	34	Oesophagus	60	6.5	Pressure	2.2
20	Male	80	3	20	Anus	60	24	Malignant	2.2
21	Male	66	3	21	Pancreas	90	4.5	Pressure	3.1

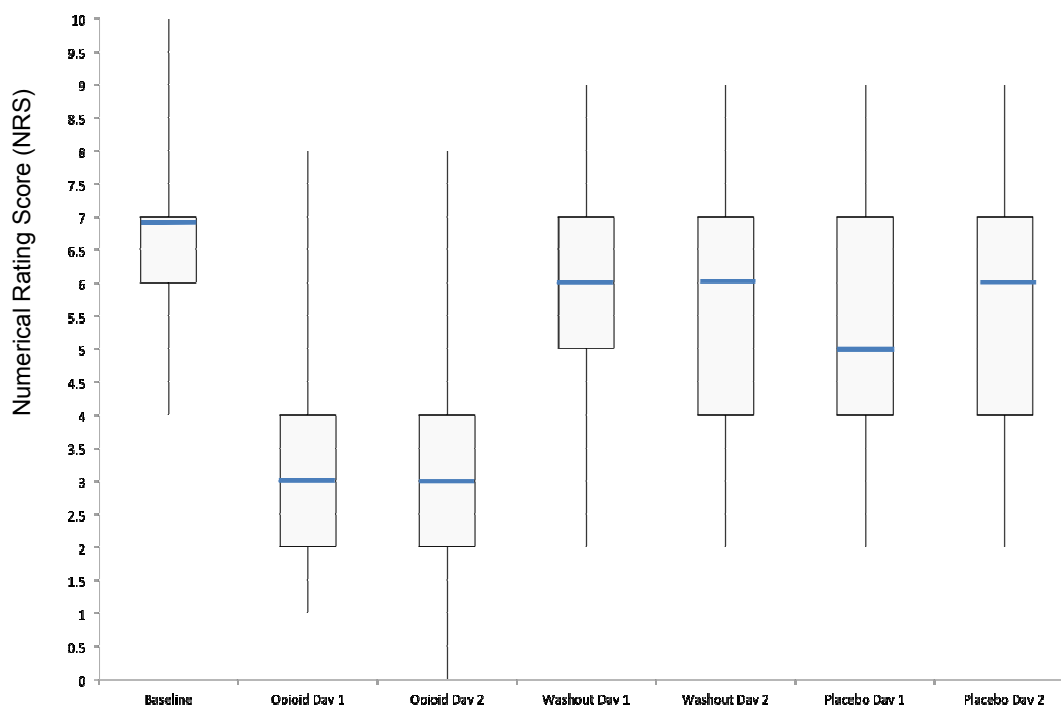
Table 5.4 Randomised double blind placebo controlled cross over study: NRS at baseline and during morphine, washout and placebo phases

Patient	First treatment	Numerical Rating Scores										Treatment Preference
		Baseline		Opioid		Washout		Placebo		Placebo		
		Day 1	Day 2	Day 1	Day 2	Day 1	Day 2	Day 1	Day 2	Day 1	Day 2	
1	Morphine	6	4	3	6	7	8	7	8	7	7	Morphine
2	Morphine	6	2	3	3	7	4	7	4	6	6	Morphine
3	Morphine	7	1	2	2	2	2	2	2	2	2	Withdrawn
4	Placebo	9	6	4	5	4	5	4	5	3	3	Placebo
5	Placebo	7	4	2	9	7	9	7	9	6	6	Morphine
6	Placebo	5	3	1	5	4	4	4	4	5	5	Morphine
7	Placebo	6	4	3	7	9	8	9	8	8	8	Morphine
8	Morphine	8	2	1	9	7	7	7	7	9	9	Morphine
9	Placebo	9	4	4	9	6	7	6	7	8	8	Withdrawn
10	Placebo	5	5	4	5	4	4	4	4	7	7	None
11	Morphine	8	3	5	4	4	4	4	4	3	3	Placebo
12	Morphine	10	3	4	9	7	9	7	9	7	7	None
13	Morphine	6	2	1	6	6	4	6	4	5	5	Morphine
14	Morphine	7	3	2	2	2	2	2	2	2	2	Withdrawn
15	Placebo	6	7	7	7	7	7	7	7	7	7	Withdrawn

Table 5.4 (Continued) Randomised double blind placebo controlled cross over study: NRS at baseline and during morphine, washout and placebo phases

Patient	First treatment	Numerical Rating Scores										Treatment Preference
		Baseline	Opioid		Washout		Placebo		Placebo			
			Day 1	Day 2	Day 1	Day 2	Day 1	Day 2	Day 1	Day 2		
16	Morphine	4	3	2	2	3	3	3	3	3	None	
17	Placebo	6	2	3	5	6	5	5	4	Morphine		
18	Placebo	7	8	8	8	8	8	8	7	Withdrawn		
19	Morphine	5	2	0	5	4	4	4	3	Morphine		
20	Placebo	7	2	1	6	5	5	6	5	Morphine		
21	Morphine	7	3	2	6	7	5	5	6	Morphine		
ITT												
Mean		6.71	3.48	2.95	5.71	5.52	5.48	5.48	5.38			
SD		1.49	1.78	1.99	2.31	1.97	2.18	2.18	2.11			
Median		7	3	3	6	6	5	5	6			
Per Protocol												
Mean		6.21	3.42	3.13	5.27	5.10	4.91	4.91	4.83			
SD		1.91	1.85	2.20	2.05	1.88	1.98	1.98	1.85			
Median		6	3	2.5	5.5	6	5	5	5.5			

Figure 5.3 Randomised double blind placebo controlled cross over study ITT population (n=21): Median, upper and lower quartiles, minimum and maximum NRS at baseline and during morphine, washout and placebo treatment periods



The primary outcome NRS comparison of morphine day 1 compared the preceding day NRS (baseline (n=11), washout day 2 (n=10)) was significant (Wilcoxon paired test, $p = 0.0004$); furthermore in 16 patients (71%) there was a ≥ 2 point reduction in NRS; the (mean \pm SD) change in NRS was 3.9 (2.9 ± 2.4) range +2 to -7.

No significant difference was seen between the NRS for placebo day 1 and that of the preceding day (baseline = 10, washout day 2 = 11) ($p = 0.36$) and of these patients, 5 (24%) had a ≥ 2 point reduction in NRS; the (mean \pm SD) change in NRS for the placebo group was 0 (0.3 ± 1.7) range +2 to -4.

The median (mean \pm SD) NRS scores for all opioid treatment days and placebo treatment days were 3.0 (2.9 \pm 1.9) and 5.0 (5.3 \pm 2.1) respectively (Mann Whitney U-test, $p < 0.0001$). No significant difference was seen between the two consecutive days washout (Wilcoxon paired test $p = 0.45$), and placebo ($p = 0.79$); a trend towards significant improvement was seen on day 2 opioid treatment compared to day 1 ($p = 0.07$).

For the ITT population a comparison of baseline and washout day 2 NRS using Wilcoxon paired test showed a significant difference ($p = 0.04$). Dividing the population between patients who started with either morphine or placebo showed a median (range) NRS for the morphine group at baseline of 7 (4-10) and washout day 2 of 6 (2-7) and comparison between the two $p = 0.06$, whereas for the placebo group the median (range) NRS was 6.5 (5-9), the paired washout day 2 was 6 (4-9) and the comparison between the two $p = 0.4$, suggesting that the washout for the morphine group may not have been complete.

For the PP population a paired comparison between the groups showed a median (range) NRS for the morphine group ($n = 9$) at baseline of 6 (4-10) and washout day 2 of 7 (3-7) and comparison between the two $p = 0.2$, whereas for the placebo group ($n = 7$) the median (range) NRS was 6 (5-9), the paired washout day 2 was 5 (4-9) and the comparison between the two $p = 0.4$ suggesting that washout day 2 could be used as a baseline for the second phase of the study as there was no difference this and the NRS at baseline for either group. An unpaired pre-washout comparison of morphine and placebo treatment arms from baseline was statistically significant to first time and second time points (Mann Whitney U Test $p = 0.0001$ and $p = 0.0005$ respectively), and for all observations combined ($p = 0.0001$).

Most patients (69%) preferred the analgesia on morphine treated days to placebo treated days. There was no difference in the patients' use of rescue medication during the two

treatment arms, the mean (\pm SD) number of daily rescue doses taken were 1.9 (1.7) during placebo and 1.8 (1.5) during morphine and 2.1 (1.8) during the washout period. ($p > 0.1$). During the trial period patients had their usual rescue medication to take, as they required. There was no difference in the patients' use of rescue medication throughout the trial; the mean (\pm SD) number of daily rescue doses taken was 2.1 (1.1) during placebo, 2.3 (1.7) during morphine treatment and 2.3 (1.8) during the washout period ($p > 0.1$).

Systemic adverse effects were monitored during the study. The number of patient reports (n), mean NRS \pm SD for nausea during placebo phase was n = 14, 0.49 ± 0.69 , washout n = 19, 1.23 ± 1.80 and during morphine n = 16, 0.57 ± 0.77 and for drowsiness during placebo phase was n = 24, 1.27 ± 31.71 , washout n = 18, 1.14 ± 1.91 and during morphine n = 21, 1.11 ± 1.39 . Although drowsiness was reported more common than nausea there was no difference in each of the symptoms during the three phases of the study ($p > 0.1$).

Patients reported local symptoms associated with the ulcer on 174 occasions during the course of the study [Figure 5.4]. None of the local adverse effects appeared specifically attributable to morphine, adverse effects were reported more frequently, during placebo treatment when compared to morphine and of borderline statistically significant ($\chi^2 = 7.7$, $p = 0.06$); no significant differences were found between morphine treatment and washout days ($\chi^2 = 2.68$, $p = 0.44$) and placebo treatment and washout days ($\chi^2 = 3.51$, $p = 0.32$).

During the course of the studies the nurses dressing the ulcers documented local and systemic adverse effects [Figure 5.5], as with patient reports, none of these specifically attributable to morphine and there was no difference comparing placebo to morphine treatment days ($\chi^2 = 0.39$, $p = 0.94$), morphine treatment and washout days ($\chi^2 = 0.72$, $p = 0.87$) and placebo treatment and washout days ($\chi^2 = 0.1$, $p = 0.99$).

Figure 5.4 Local adverse effects during the placebo, washout and morphine phases of the randomised controlled study were recorded by patients (n=15)

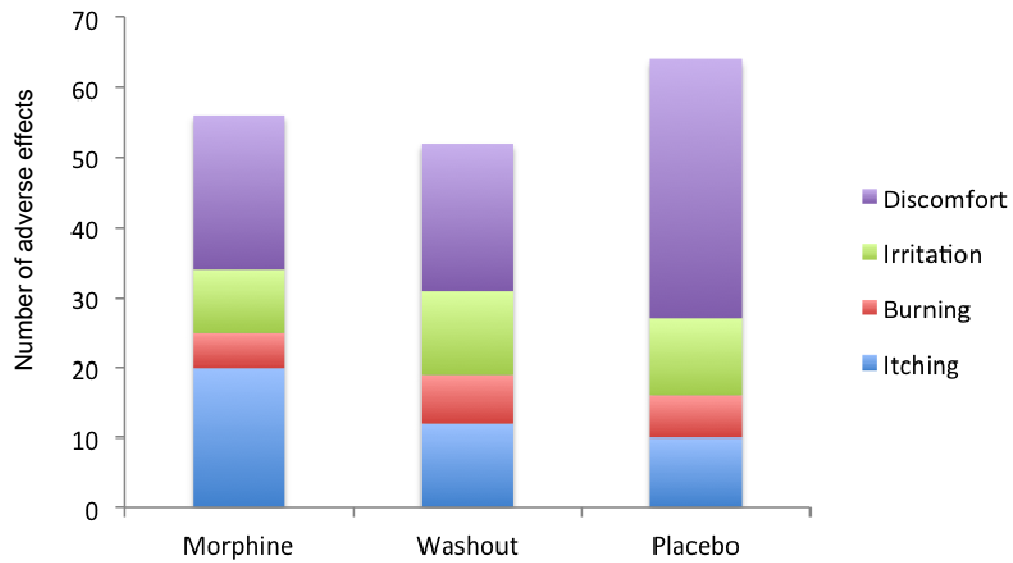
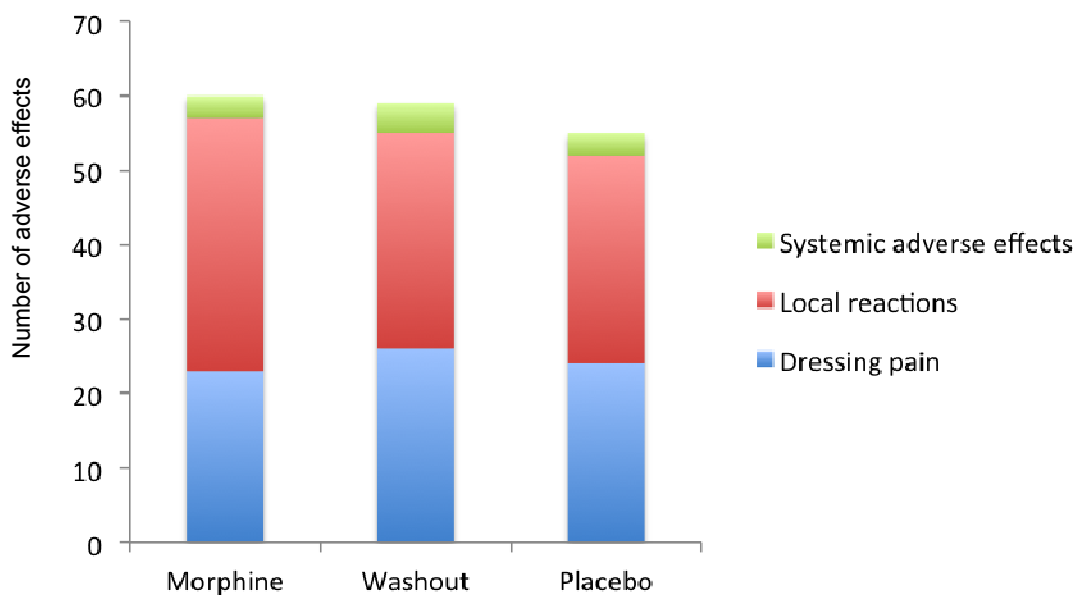


Figure 5.5 Nurses reported dressing related pain, local reactions or systemic adverse during the placebo, washout and morphine phases of the randomised controlled study in patients (n=13)



At the end of the study the median (mean \pm SD) ulcer area was 16.2 (10.1 \pm 13) and little changed from the start of the study ($z = 0.87$, $p = 0.38$); there was no difference in the ulcer grade at the end compared to the start of the study.

5.6.3 Discussion

Like the pilot study, this study suggested that patients with painful pressure sores found morphine to be a more effective analgesic than placebo. Morphine 10 mg appeared effective across a wide range of background opioid dose, for example one patient was opioid naïve whereas another was taking the daily equivalent of 240 mg oral morphine. It is possible that patients responding less favourably to topical opioids may have benefitted from an increased dose of morphine or more frequent applications during the course of the day. The same may also be true for ulcer size, for example patient 9 with an ulcer of 22.4 cm² demonstrated small differences in NRS scores and reported no preference between the different treatment days. However the ulcer sizes of patients reporting a preference for morphine (second study) varied almost tenfold (4.5-38 cm²).

In order to preserve benefit of randomisation all randomised participants were included in the ITT analysis, which is widely recommended as the preferred analysis strategy because it avoids bias associated with non-random loss of participants (Hollis & Campbell 1999; Herman et al. 2009). Data were missing for five patients randomised to order of treatment but did not complete the study. To account for these missing outcomes the “last observation carried forward” was used, where missing values were replaced by the last known value before the patient dropped out of the study. Although a simple and widely used process, it has been suggested that this method can introduce bias (Molnar et al. 2008) and has been criticised as no allowance is made for the uncertainty of imputation (Ware 2003; Streiner 2002; Lane 2008).

Missing data could result in the ITT analysis underestimating the potential benefit of the treatment and other analyses, such as a PP analysis, may be considered and are therefore included in the results. Indeed the ITT analysis in this study appeared to show a carry over

effect of morphine, and not placebo, to the washout days as relatively small NRS values were being carried forward to account for missing data; this was not seen in the PP analysis. Given the difficulties with assumptions made in the various analytical methods the CONSORT checklist has dropped the specific request for ITT analysis in favour of a clear description of exactly who was included in each analysis (Moher et al. 2010).

Opioid receptors have been demonstrated in peripheral sensory nerves and are activated by either endogenous or exogenous opioids allowing the possibility to provide localised analgesia, avoiding systemic analgesia thus minimising systemic adverse effects. The distinction therefore is drawn between this local effect associated with topical application and the more widely recognised systemic analgesic effect associated with transdermal delivery of opioids such as fentanyl. No systemic adverse effects specifically attributable to morphine were reported, including three opioid naïve patients, supporting the possibility of a local mode of action.

Morphine applied topically to painful ulcers was generally well tolerated by patients, although mild local reactions were described during the study. In this, and most other studies, the opioid has been mixed with IntraSite gel, a hydrogel designed for debridement of necrotic tissue and for wounds that are granulating and epithelialising. When in contact with the wound, IntraSite absorbs excess exudates and produces a moist environment at the surface of the wound. Although generally well tolerated, it is possible that the local symptoms described by patients in both studies were due to IntraSite gel (propylene glycol, is a potential irritant and sensitising agent), as the local reactions were reported during both morphine and placebo treated days.

The pain from cutaneous ulcers is often complex with features of both nociceptive and neuropathic pain. In the past it was felt that neuropathic pain was non responsive to opioids (Amer & Meyerson 1988) and the concept of opioid-responsive and opioid-non-responsive pain were often equated with nociceptive and non-nociceptive pain (Hanks 1991; Hanks & Forbes 1997). The subsequent finding that both central and peripheral neuropathic pain can respond to opioids (DelleMijn 1990; Rowbotham et al. 2003), has led to the concept of opioid responsiveness, defined as the degree of analgesia obtained following the escalation of the dose to the point of analgesia or intolerable adverse effects (Portenoy et al. 1990). In some cases it appears that although the neuropathic pain is opioid responsive, systemic adverse effects limit titration to an effective dose (Eisenberg et al. 2006); topical administration of opioids avoids this potential systemic problem.

The major advantage of the crossover design used in these studies was that it allowed within subject comparison between treatments (each subject serves as their own control) by removing the between subject variability from the comparison. The sample size was not calculated beforehand as we had insufficient data upon which to base the calculation. Using the data from the second study that indicated the change in pain score was normally distributed with a standard deviation 1.9, 12 subjects would be required to achieve a 90% power for detection of a clinically meaningful NRS difference of 2 at the 5% level of significance. As 16 patients were studied, the power was greater than 90%.

There is a growing literature on the utility of opioids applied topically to painful cutaneous ulcers. Since undertaking the systematic review for this project (Chapter 2) an updated review using the same search strategy undertaken in September 2010 identified a further 14 studies, eleven case reports (Ballas 2002; Abbas 2004; Ashfield 2005; Durán et al. 2005;

Table 5.5 Studies identified in the updated systematic literature review (2002-2010)

First Author	Design	Patients	Intervention	Outcome
Ballas 2002	Case report	2 patients with ulcers from sickle cell anaemia	5 mg oxycodone mixed with the debridement ointment or 100mg pethidine mixed with xylocaine ointment. Both opioids were dissolved in water before mixing	Almost immediate and complete relief of pain; in one patient systemic analgesia was decreased
Flock 2003	RCT	13 cancer patients with grade II or III pressure ulcers; 7 completed	0.1% diamorphine and IntraSite gel applied daily for 3 days vs. IntraSite gel daily for 3 days with 2 day washout	Statistically significant improvement in VRS at 1 and 12 hours (p<0.05)
Abbas 2004	Retrospective case series	17 cancer patients with grade II or greater painful pressure sores	5-10mg diamorphine in IntraSite gel administered every 12 – 24 hours	Statistically significant improvement in mean VAS scores (p<0.002)
Ashfield 2005	Case report	1 cancer patient with 2 painful pressure ulcers	0.1-0.125% Diamorphine IntraSite gel applied daily	Subjective pain relief reported by patients
Dúran 2005	Case report	1 patient with non-malignant ulcer	Morphine 10 mg in 8g IntraSite gel applied daily	The NRS decreased to 0 within 15 minutes and pain controlled for 24 hours No adverse effects were recorded
Gallagher 2005	Case reports	4 patients with painful malignant and non-malignant ulcers	Mixture of 100mg methadone in 10g Stomahesive powder or DuoDerm gel applied daily; approx. 25mg methadone per 15cm ² wound	Pain relief reported in 3 (75%) patients
Platzter 2005	Case reports	6 patients, 1 with painful skin ulcer	Morphine gel 0.1% applied several times daily	NRS fell from 8 to 3 within one hour of application, and remained for up to 4 hours. No adverse effects were observed.

First Author	Design	Patients	Intervention	Outcome
Porzio 2005	Case reports	5 patients with painful malignant and non-malignant ulcers	10mg morphine sulphate in 8g IntraSite applied three times daily	Improvement in post treatment NRS. No local or systemic adverse effects reported
Vernassiere 2005	RCT	24 patients with painful chronic skin ulcers randomised, 18 entered 14 completed	10mg morphine in 15g IntraSite gel vs. Saline mixed with IntraSite gel applied daily	No statistically significant difference in NRS between active and placebo over 5 days
Tran 2007	Case report	1 patient with painful malignant ulcer	10g morphine sulphate in 8g neutral water based gel applied twice/three times daily as needed	Reduction in NRS
Zeppetella 2007	Case reports	4 patients with malignant ulcers	10-20mg morphine in 8g IntraSite gel once/three times daily	All patients reported NRS reduction following treatment. No local or systemic adverse reactions
van Ingen 2008	Case report	1 patient with painful ulcer associated with systemic sclerosis	Morphine 0.5% gel four times daily	Reduction in VAS from 80 to 40 and reduced need for subcutaneous morphine.
Jansen 2009	RCT	32 patients with arterial ulcers recruited; 9 completed study	Three treatments random cross over: 0.5% morphine hydrogel plus a SC placebo infusion, placebo gel plus a SC infusion of 5mg morphine over six hours and a placebo gel plus a SC placebo infusion.	Statistically significant different NRS between baseline and treatment (range 0.9-1.4) but not sufficient to be clinically relevant
Barker 2009	Case report	1 patient with pyoderma gangrenosum	10-20mg morphine in 8g IntraSite gel applied four times a week	Reduction in pain within an hour of application

Gallagher et al. 2005; Platzer et al. 2005; Porzio et al. 2005; Tran & Fancher 2007; Zeppetella et al. 2007; van Ingen et al. 2008, Barker 2009) and three randomised controlled trials (Flock 2003; Vernassiere et al. 2005; Jansen et al. 2009) [Table 5.5], recruiting a total of 112 patients; a further 26 patients were recruited in the aforementioned efficacy studies.

Flock (2003) recruited 13 hospice patients with grade II or III pressure ulcers that were randomly assigned to two randomised double blind treatment arms: three days of IntraSite gel followed by three days of diamorphine gel (a 0.1% w/w mixture of diamorphine in IntraSite gel), or vice versa, with two days washout period. Treatment was applied once daily and all pre-trial medication was continued. Ulcer pain was assessed before and one and 12 hours after gel application by nursing staff using a five point VRS (none, mild, moderate, severe or overwhelming); nurses checked local and systematic adverse effects once daily.

Seven patients completed the study and pain scores improved significantly at one ($p = 0.003$) and at 12 hours ($p = 0.005$) after diamorphine gel application compared with baseline. Six patients each had improved pain scores both one and 12 hours after diamorphine gel application. Four were pain free after one hour and three after 12 hours. One patient experienced symptoms of opioid toxicity, including drowsiness, nightmare, hallucinations and myoclonus during the course of the study, however her dose of transdermal fentanyl had been increased the day before recruitment and symptoms resolved once the fentanyl dose was reduced. The study recruited similar patients and used similar methods to those employed in our studies although the opioid was different. Given the evidence that diamorphine degrades to morphine and 6-monoacetylmorphine, both of which may have contributed, in some part, to the analgesia.

Not all randomised trials have reported positive results. Vernassiere et al. (2005) recruited 26 patients with painful chronic skin ulcers $\leq 150 \text{ cm}^2$ to a controlled double-blind randomised study. Patients received either 10 mg of morphine hydrochloride or water mixed with 15 g of IntraSite gel at a fixed time daily for five days. Pain was assessed using NRS before, immediately after, one hour and 12 hours after treatment. All patients received opioids for mild to moderate pain and had access to rescue treatment. During the five days of treatment there was no statistically significant difference between the two groups' assessment of pain relief: patients on the morphine group assessed the overall analgesic efficacy at 5.5 over five days, versus 5.6 for patients in the placebo group. Systemic tolerance was noted to be good. Although the opioid and hydrogel were similar to that used in our study the methodology was different, including randomisation, opioid administration method and assessments. Furthermore there was a significant difference in the pre-treatment pain scores in the two treatment arms ($p = 0.03$). The two groups were treated separately without cross over and the final morphine group included nine patients whereas the placebo group had five patients; the process of randomisation was also unclear. The concentration of morphine tested was half that used in our pilot and extended studies.

Jansen et al. (2009) reported a in a double-blind, placebo-controlled, three-way crossover pilot study involving nine patients to assess the efficacy of topically applied 0.5% morphine in hydrogel for painful arterial leg ulcers. All patients had a baseline NRS of at least 5. The three treatments randomised on three consecutive days were morphine hydrogel plus a subcutaneous placebo infusion, placebo gel plus a subcutaneous infusion of 5 mg morphine over six hours and a placebo gel plus a subcutaneous placebo infusion. Each treatment lasted one day and pain was assessed during the first 24 hours after application of the hydrogel and the start of the subcutaneous infusion. There was a statistically significant difference between average baseline pain scores and those reported during treatment, but this difference was not

clinically significant. The three treatments did not differ in terms of the pain relief provided suggesting that topical application of morphine does not have a clinically relevant analgesic effect in patients with painful arterial leg ulcers.

The available data suffer from limitations common in palliative care studies namely small patient numbers and high attrition rates, the latter often due to the unpredictable nature of malignant disease and poor estimates of life expectancy (McWhinney et al. 1994; Kinzbrunner et al. 1995; Rinck et al. 1997; Smeenk et al. 1998). The patients recruited to our study were generally elderly (average age 77) and had poor performance status (average ECOG 3.1 i.e. capable of only limited self-care, confined to bed or chair for more than 50% of waking hours) and were therefore typical of many hospice admissions. Other challenges include patient vulnerability, obtaining informed consent, conflict between research and clinical roles and difficulties faced by patients in evaluating the risks and benefits of research and in particular the burden of research upon the participant. Not all these problems are unique to palliative care and have been successfully addressed in other areas of medical research (Cassarett & Karlawish 2000).

5.6.3.1 Other reports of topical opioid application to cutaneous wounds

In addition to the chronic wounds identified in the systematic review, morphine has been applied to chronic venous ulcers, and acute wounds including burns, oral mucositis, the pain of photodynamic therapy, and in children with epidermolysis bullosa; results have been variable.

Venous leg ulcers affect 1% in the adult population and up to 5% in the population over 65 years of age (Gottrup & Karlsmark 2005). When they become painful, venous ulcers often limit patient mobility and simple daily activities, furthermore dressings and dressing changes can further increase discomfort. A randomised, placebo-controlled, crossover pilot study (Bastami

et al. 2011) where 21 patients were randomly assigned to receive either morphine or placebo, failed to show an overall statistically significant difference between the two groups. In a systematic literature review of randomised controlled trials evaluating locally applied therapies to relieve venous leg ulcer pain (Briggs & Nelson 2010), although one study had been identified (Vernassiere et al. 2005), also identified in the review included in this chapter, it included people with both leg and pressure ulcers and could not therefore be included; no other studies were found to support the use of topically applied opioids for either background or dressing related pain.

The pain from burns is one of the most distressing symptoms and yet difficult to manage. Common treatment options include oral or parenteral opioid although topical opioid have also been tried. In a double-blind, placebo-controlled study with four patients morphine-infused silver sulfadiazine cream reported lower average (range) pain ratings than placebo, 2.1 (0-7) vs. 5.6 (2-8) compared to placebo ($p = 0.001$), and had a lower average oral morphine consumption per half day, 42.9 mg vs. 55.3 mg ($p = 0.07$). In a separate placebo-controlled three-treatment randomised controlled trial, 59 patients were randomly allocated to receive a dressing containing IntraSite gel and morphine sulphate, IntraSite gel and water or the conventional Jelonet dressing (Welling 2007). No significant differences were observed between the pain scores or comfort ratings of the three treatments.

Oral mucositis is one of the most common and debilitating adverse effects of radiotherapy and/or chemotherapy and despite many treatment strategies, no gold standard exists (Clarkson et al 2010). In a two-phase study, 10 patients were first randomized to receive 15 ml of either 1% or 2% morphine solution followed by an efficacy an open safety phase with 22 patients; in addition morphine serum concentrations were measured in five patients. The first phase suggested a dose-response relationship for topical morphine as 2% morphine solution

showed better pain relief than those with 1‰ ($p = 0.02$). Therefore in the second phase, patients received 2‰ morphine solution and reported time to good ($\geq 50\%$) or to complete (100%) pain relief was 28 (± 12) minutes after the first mouthwash, and the duration of relief was on average 216 (± 25) minutes. Six patients needed supplementary analgesia after, on average 1.18 (± 0.8) days. No systemically active detectable concentrations of morphine were found; very mild-mild intensity burning/itching sensation was reported as a local adverse effect. The same group enrolled 26 patients with WHO \geq Grade 2 painful mucositis, randomly assigning them to either as 2‰ morphine mouthwash or a mixture of equal parts of lidocaine, diphenhydramine, and magnesium aluminium hydroxide (Cerchietti et al. 2003). When compared to the alternative mixture, morphine resulted in significantly lower pain intensity and duration ($p = 0.03$, $p = 0.04$ respectively), fewer local adverse effects ($p = 0.007$) and none of the morphine patients required step three opioids. Furthermore there was a significant difference in duration of severe functional impairment ($P = 0.017$). In another randomised double-blinded crossover trial, patients suffering from radiotherapy- and/or chemotherapy-induced oral mucositis, patients were assigned to either the as 2‰ morphine solution or a placebo mouthwash (Vayne-Bossert et al 2010). Duration of pain relief following morphine was 123.7 minutes suggesting a possible analgesic effect of topical morphine in line with previous studies. None of the studies cited above were identified in the systematic review of interventions for treating oral mucositis for patients with cancer receiving treatment (Clarkson et al. 2010)

Morphine gel has been tried on the management of pain resulting from photodynamic therapy, a well-established treatment for actinic keratoses and basal cell carcinomas where frequently adverse effects are pain and post-treatment erythema and oedema. In a randomised, double-blind, placebo-controlled study involving 28 patients with either actinic keratoses or basal cell carcinomas, 3% morphine gel failed to show significant pain relief when

compared with placebo gel ($p > 0.23$) (Skiveren et al. 2006). The authors suggest that hat opioid receptors may not be involved in the pain induced by photodynamic therapy.

Most identified studies have been in adults, however the use of topical morphine has been described in children with epidermolysis bullosa, a hereditary bullous disorder of the skin, in which minimal trauma causes chronic, severe and extremely painful blistering (Watterson et al. 2004). The cases of a 13 and a 16 year girl were reported where 10 mg morphine sulphate was mixed with 15 g of IntraSite gel and a dose of morphine equivalent to 0.2 mg/kg was used. Ulcer pain assessed using a VAS fell in both patients at one hour. The 16 year old was opioid naive but noted no adverse effects after using the morphine gel. Both patients continued to use the gel with good effect for between one and five months

In summary these data are variable and have employed different opioid concentrations, carriers, and administration frequencies. On the whole, however, these results are less encouraging than the studies identified in the systematic review

The long term effects of topically applied opioids require further investigation. There are recent data from animal studies suggesting that topical administration of opioids may impair wound healing by inhibiting the peripheral release of neuropeptides and reduce inflammation (Rook et al. 2007; Rook & McCarson 2009), although these effects may be time-dependent and if demonstrated in patients may require strategies such as the timing of the administration and the addition of adjuvant drugs to optimise topical opioid administration (Rook et al. 2008). Conversely other animal studies have suggested that opioids can accelerate wound healing by up-regulating nitric-oxide synthase (Poonawala et al. 2005). The duration of our studies were short and may not have been sufficient to demonstrate some of the longer term adverse effects of opioids, furthermore the potential for palliative care to improve wound healing and

the quality of life for patients and families living with chronic wounds is also recognised (Schulz et al. 2002; Ferris et al. 2007).

Other long-term effects of opioids include immune suppression (Vallejo et al. 2004). The relationship between pain and the immune system is well described, in particular how the inflammatory response is amplified by migration of leucocytes in the inflamed tissues by the production of cytokines, chemokines, growth factors and a fall in pH (Rittner et al. 2008). The short duration and design of this study do not allow any conclusions to be drawn on the immune suppressive effects of topically applied opioids.

The prolonged application of opioids can sometimes lead to tolerance (Furlan et al 2008). Although this is often a concern in chronic non-cancer pain management it is considered less of a clinical problem in the palliative care setting (Collin et al. 1993; Zech et al. 1995; Grond et al. 1996). There are experimental data that suggest long term exposure of peripheral opioid receptors to opioids may result in tolerance however the presence of inflammation appears to reduce this effect (Zöllner et al. 2008). As with immune suppression the duration and design of this study did not allow it to draw any conclusion on tolerance.

5.6.4 Summary

Two randomised, double blind, placebo controlled, crossover studies are described that are consistent with the previous open studies in the literature that have reported an analgesic effect when morphine has been applied topically to painful cutaneous ulcers. The patient numbers in both studies are small and these data, therefore, should be interpreted cautiously. In particular, it is not possible to draw conclusions about the type, grade, and area of ulcer that responds best to topical opioid application, as other published randomised controlled studies with different methodologies have reported different outcomes. The duration of the studies

was short and it was not possible to determine whether tolerance is a feature in topical opioid administration. Furthermore the conclusions cannot be applied to necrotic and infected ulcers as they were excluded from the study, nor the use of a carrier other than IntraSite gel.

Chapter 6: Bioavailability of morphine applied topically to cutaneous ulcers

6.1 Introduction

Morphine is the most commonly used opioid applied to painful cutaneous wounds, although other opioids, including diamorphine, oxycodone, hydromorphone and fentanyl have been used. The rationale for the use of topical opioids is that their site of action is local and not systemic. To confirm this would require evidence of the limited systemic absorption when the opioid is applied topically to a cutaneous wound. Despite the increased use of topical opioids, there are no pharmacokinetic studies evaluating this route in palliative care patients. A challenge with such a study may be the low plasma morphine and metabolite concentrations resulting from topical administration, requiring a sensitive analytical method such as liquid chromatography with electrochemical detection.

Chromatography is the collective term for a set of laboratory techniques used for the separation of mixtures. It involves a sample (or analyte) being dissolved in a mobile phase (gas or a liquid). The mobile phase is then forced through an immobile, immiscible stationary phase. The phases are chosen such that components of the sample have differing solubility within each. A component which is quite soluble in the stationary phase will take longer to travel through the column than a component which is less soluble in the stationary phase but very soluble in the mobile phase. As a result of these differences in mobility, sample components will become separated from each other as they travel through the stationary phase.

In 1906 the Russian chemist and botanist Mikhail Semyonovich Tswett devised an absorption method for separating the pigments of green leaves (Berezkin 2001). He was able to identify

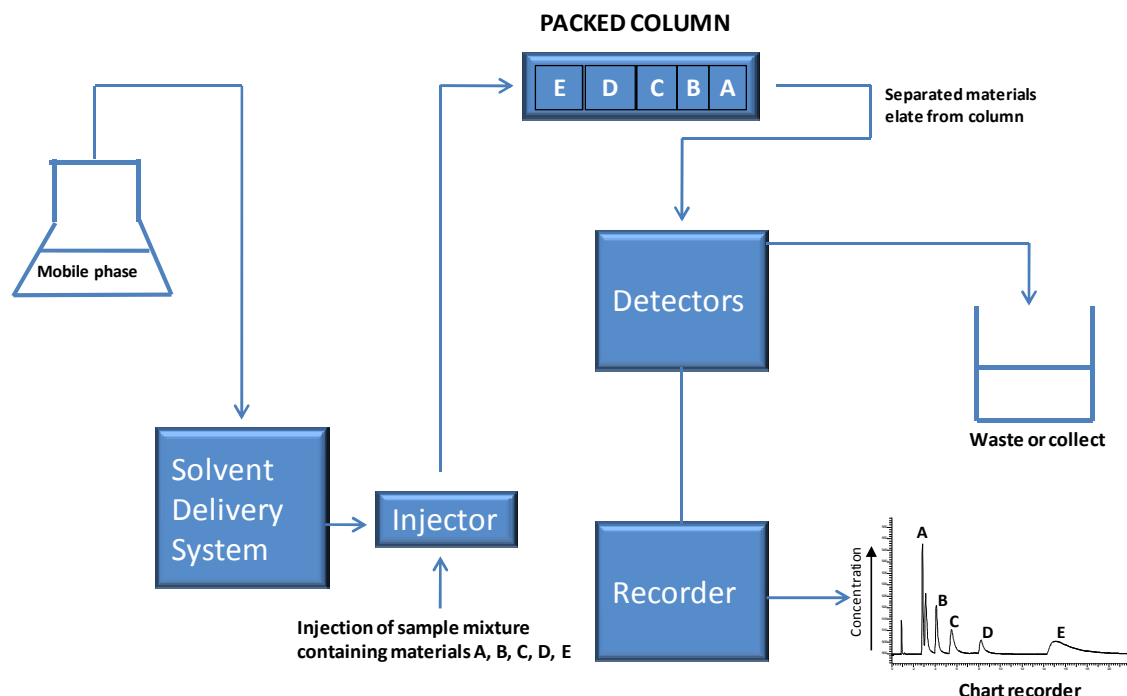
six pigments by grinding leaves in petroleum ether and allowing the liquid to trickle down a glass tube filled with powdered chalk or alumina. He named the process chromatography (colour development) and the technique, although not widely used in his own lifetime, has since become essential in analytical laboratories (Gehrke et al. 2001).

Three types of chromatography are routinely used:

- Column chromatography where the stationary phase is a solid adsorbent placed in a glass or stainless steel column, the analytes is loaded on top of this column and the mobile phase is a solvent poured or pumped through on top of the loaded column. As the solvent flows down the column, the components of the analyte distribute between the adsorbent and the solvent, thus separating the components of the mixture.
- Thin Layer Chromatography where the stationary phase is an adsorbent fixed to an aluminium, glass, or plastic plate and the analyte is loaded near the bottom of the plate. The plate is placed in a reservoir of solvent so that only the bottom of the plate is submerged. As the solvent moves up the plate it causes the components of the analyte to distribute between the adsorbent on the plate and the moving solvent.
- Gas Chromatography where the stationary phase is a high-boiling point liquid packed into a long, narrow glass or metal column and the analyte is loaded into the beginning of this column; the mobile phase is an inert gas which continuously flows through the column. The components of the analyte distribute between the stationary liquid and mobile gas phase moving through the column.

High-performance liquid chromatography (HPLC) is a chromatographic technique that utilises different types of stationary phases, a pump that moves the mobile phase and mixture

Figure 6.1 Diagram to illustrate the components of an HPLC system: the sample containing materials A, B, C, D and E is injected into the column, the separated solutes are detected as they emerge from the columns by a sensitive detector, and the detector signal is recorded to give a quantifiable record.



through the column, and a detector to provide a characteristic retention time for the analyte [Figure 6.1]. It is a form of liquid chromatography that utilizes smaller column size, smaller media inside the column, and higher mobile phase pressures. With HPLC, a pump (rather than gravity) provides the higher pressure required to move the mobile phase and analyte through the densely packed column (Knox 1978). In reversed-phase HPLC compounds are separated based on their hydrophobic character. The stationary bed is hydrophobic in nature, while the mobile phase is a polar liquid. Structural properties of the analyte molecule play an important role in its retention characteristics. In general, an analyte with a larger hydrophobic surface area results in a longer retention time whereas polar analytes reduce retention as they are well integrated into the more polar mobile phase.

6.2 Aims of bioavailability study

The aim of this study was to determine the bioavailability of morphine and its metabolites, morphine- 6-glucuronide (M6G) and morphine-3-glucuronide (M3G), using HPLC, following the topical application of morphine sulphate mixed in IntraSite gel to cutaneous ulcers in hospice inpatients.

6.3 Methods

This was a randomised, open label cross over study; ethical approval for the study was obtained from the local ethics committee. Six adult hospice patients were recruited into the study. Patients were eligible if they had skin ulcers (larger than 2 cm in diameter and 0.5 cm in depth) that were neither infected nor covered with necrotic tissue. Patients were required to be morphine, codeine, diamorphine or hydromorphone naïve; fentanyl and tramadol were the only opioids permitted, as they and their metabolites do not interfere with the HPLC assay for morphine.

Following written informed consent, patients received either morphine sulphate in IntraSite gel applied topically to their ulcer or morphine sulphate administered subcutaneously over four hours, followed by the alternate treatment (topical or subcutaneous); the two treatments were separated by a washout period of one day. The order of treatments was randomised using a table of random numbers.

The topical morphine mixture was prepared by thoroughly mixing morphine sulphate injection BP 10 mg (Celltech Pharmaceuticals, Berkshire, UK) with IntraSite gel 8 g (Smith & Nephew Healthcare Ltd, Middlesex, UK) in a sterile galipot; this dose of morphine was chosen as it is commonly used in clinical practice. The ulcer was first cleaned with sterile water, after which the morphine mixture was applied directly to the wound and then covered with a Tegaderm

dressing. The opioid was kept in contact with the wound for 24 hours. Venous blood samples were taken from an indwelling cannula immediately prior to the application of morphine, and then at 1, 2, 4, 6, 8, 10, 12, and 24 hours afterwards.

The subcutaneous morphine infusion was prepared by diluting morphine sulphate 10 mg in water for injection to a volume of 10 mL in a plastic syringe. The syringe was then attached to a syringe driver (Graseby MS16a) and connected to an infusion set with the butterfly needle inserted in the upper forearm. The infusion set was primed with the morphine solution and the whole amount delivered over four hours. Venous blood samples were collected immediately prior to starting the infusion and then at 1, 2, 4, 6, 8, 10, and 12 hours after commencement. All blood samples were separated by centrifugation (1000g for 10 minutes) within 30 minutes of collection and the plasma then stored at -40°C until analysis.

6.3.1 Pharmacokinetic assessment

Morphine, M3G, and M6G (all Sigma chemicals, Poole UK) were analysed using a previously reported method (Joel et al 1988), involving sample clean-up using C8 cartridges (1 cc/100 mg Varian, Anachem, Luton, Beds) followed by reverse-phase HPLC with electrochemical and fluorescence detection. Extraction cartridges were conditioned with methanol (1.5 mL), 10 mM sodium dihydrogen phosphate, pH 2.1 with 10% acetonitrile (1.0 mL) and water (1.5 mL). Plasma (0.75 mL) was buffered with 500 mM ammonium sulphate, pH 9.3 (2.25 mL), and 2.5 mL of this mixture loaded onto the cartridge. The cartridge was then washed with 5mM ammonium sulphate, pH 9.3 (5.0 mL), and water (0.2 mL). Morphine and its metabolites were eluted with 10 mM sodium dihydrogen orthophosphate pH 2.10 with 10% acetonitrile (0.80 mL).

Separation was achieved using an Apex 5 μ C18 column (Jones Chromatography, Hengoed, Wales) fitted with a 2-cm Apex ODS 10 μ m precolumn. Morphine and M6G were detected by electrochemical detection and M3G by fluorescence detection. Approximate retention times for M3G, M6G, and morphine were 4, 5.5, and 10 minutes respectively, with lower limits of quantitation (LLQ) of 3 nM/L (1.1 ng/mL) for morphine, 2 nM/L (1 ng/mL) for M6G, and 40 nM/L (20 ng/mL) for M3G. Between-run variability for this assay at 100, 800, and 3500 nM/L M3G and 10, 80, and 350 nM/L morphine and M6G is less than 10%.

Pharmacokinetic parameters for morphine, M3G and M6G were derived using non-compartmental methods in Kinetica (Innaphase Corp, Philadelphia, PA). The area under the concentration time curve (AUC) was calculated using the trapezoidal method as the sum of linear areas up to the maximum concentration and logarithmic areas from C_{max} to the last time point (t_n). AUC was extrapolated out to infinity using the concentration at the last time point and the elimination rate constant (λ_z). C_{max} and t_{max} were the measured values. The elimination half-life was calculated as $0.693/\lambda_z$, the apparent clearance (CL) as dose divided by $AUC_{0-\infty}$ and the apparent volume of distribution as dose divided by the product of $AUC_{0-\infty} \times \lambda_z$. The bioavailability of morphine, and apparent bioavailabilities of M3G and M6G, after topical morphine were calculated as $AUC_{0-t_n, TOPICAL}/AUC_{0-t_n, INFUSION} \times 100$.

6.4 Results

6.4.1 Patients

Three male and three female hospice in-patients entered the study [Table 6.1]. Most patients had advanced cancer and all but one were receiving regular analgesia. The mean (range) surface area of the ulcers was 20.4 cm² (4.5-60); one ulcer was of malignant aetiology, the remainder were benign. Morphine, M6G and M3G were below the LLQ in all samples prior to the administration of subcutaneous or topical morphine.

Table 6.1 Morphine bioavailability study: patient and ulcer characteristics

Patient	Sex	Age	Diagnosis	Ulcer size	Analgesia
1	M	87	Ca Colon	13 cm ²	Paracetamol 1g prn
2	M	61	MS*	9 cm ²	Paracetamol 1g prn
3	M	80	Ca prostate	5 cm ²	Fentanyl-TTS 25mcg/h, Diclofenac 50mg tds, Paracetamol 1g qds
4	F	73	Ca breast	23 cm ²	Tramadol 100mg tds, Ibuprofen 400mg tds
5	F	70	COPD*	14 cm ²	None
6	F	67	Ca Lung	60 cm ²	Paracetamol 1g qds, Tramadol 200mg bd

*MS= Multiple sclerosis; COPD = Chronic Obstructive Pulmonary Disease

6.4.2 Subcutaneous morphine

Mean plasma concentrations of morphine, M6G and M3G in all six patients after subcutaneous morphine are shown in Figure 6.2. Morphine was detected in the first post-treatment sample (1 hour) in all patients and was still detectable in four patients at 12 hours. Peak morphine concentration was measured at four hours in five patients and at two hours in the remaining patient (56.5 nmol/L at two hours vs. 50.0 nmol/L at four hours). M6G was first detected at one hour in five patients and at two hours in one patient, and was still detectable in all patients at 12 hours. M3G was detected at one hour in one patient, two hours in four patients, and three hours in the remaining one patient. As with M6G, M3G remained detectable in all patients at 12 hours. Peak metabolite concentrations occurred between four and eight hours (median t_{max} was four hours for M6G and four and a half hours for M3G). Pharmacokinetic parameters for morphine, M6G and M3G are shown in Tables 6.2 & 6.3.

Figure 6.2 Plasma morphine, M6G and M3G concentration in 6 patients after 10 mg subcutaneous morphine infused over 4 hours (mean + SD).

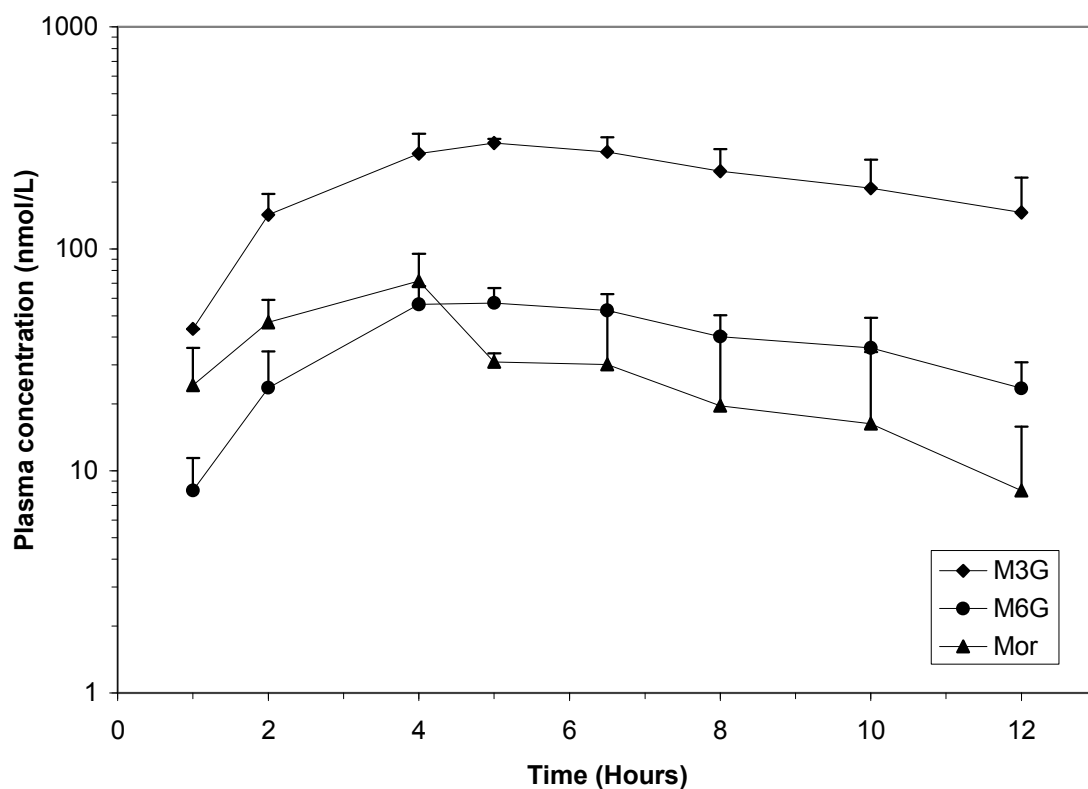


Figure 6.3 Plasma morphine and M6G concentrations in patient 6 after 10 mg topical morphine in IntraSite gel.

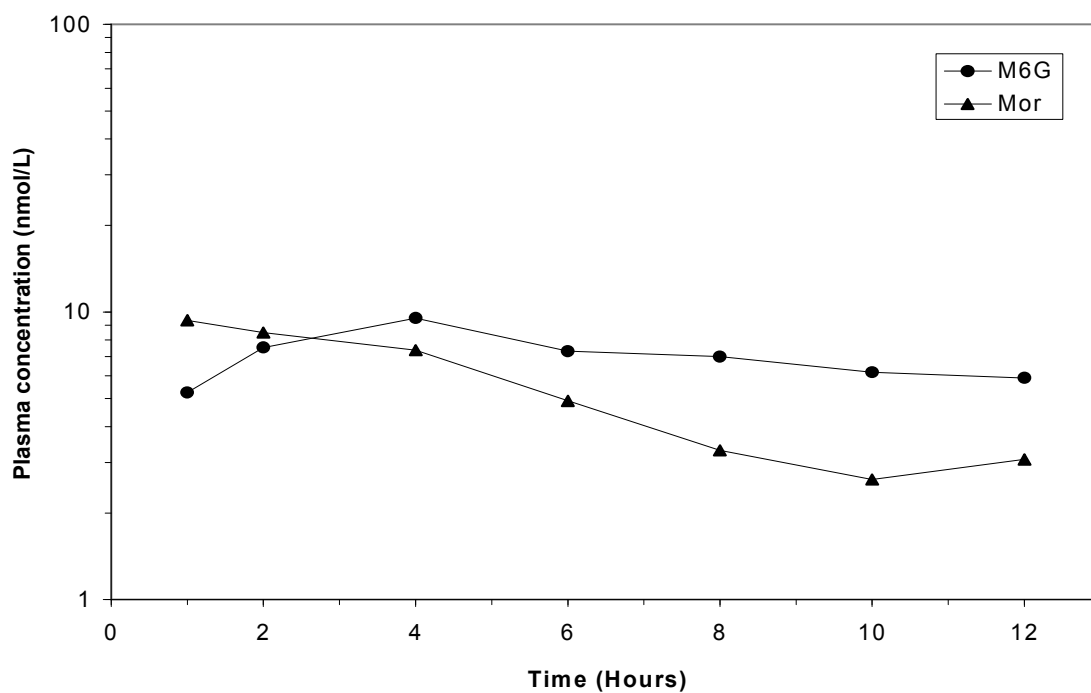


Table 6.2 Pharmacokinetics and bioavailability data for subcutaneous and topically administered morphine in all study patients

Subcutaneous Morphine									
M3G					M6G				
Study	Cmax	Tmax	AUClast		Cmax	Tmax	AUClast	Cmax	Tmax
Unit	nM/L	Hrs	nM/l.hr		nM/L	Hrs	nM/l.hr	nM/L	Hrs
1	297	8.0	2128		58.5	8.0	409	87.9	4.0
2	312	6.0	2077		61.9	4.0	360	111.0	4.0
3	329	4.0	2688		53.1	4.0	415	53.0	4.0
4	244	4.0	2485		61.8	4.0	591	64.2	4.0
5	348	4.0	2539		71.4	6.0	525	62.7	4.0
6	288	5.0	2118		54.3	4.0	402	56.5	2.0
Mean	303	5.2	2339		60.2	5.0	450	72.6	3.7
SD	36	1.6	263		6.6	1.7	88	22.5	0.8

Topical Morphine									
M3G					M6G				
Study	Cmax	Tmax	AUClast		Cmax	Tmax	AUClast	Bioavail.	
Unit	nM/L	Hrs	nM/l.hr		nM/L	Hrs	nM/l.hr	%	
1	*	*	*		*	*	*	*	*
2	*	*	*		*	*	*	*	*
3	*	*	*		*	*	*	*	*
4	*	*	*		*	*	*	*	*
5	*	*	*		*	*	*	*	*
6	*	*	*		9.5	4	82	21	56

Table 6.3 Pharmacokinetics of morphine and its glucuronides following subcutaneous and topical administration of morphine sulphate

	Morphine	M6G	M3G
<i>Subcutaneous morphine (n=6)</i>			
C _{max} (nmol/L)	72.6 ± 22.5	60.2 ± 6.6	303 ± 36
t _{max} (hr)	4 (2-4)	4 (4-8)	4.5 (4-8)
AUC _{0-tn} (nmol/l.hr)	326 ± 90	450 ± 88	2339 ± 262
AUC _{0-INF} (nmol/L.hr)	356 ± 105	588 ± 82	3652 ± 850
Apparent CL (mL/min)	1295 ± 267	-	-
Apparent V _d (L)	281 ± 52	-	-
Elimination t _{1/2} (hr)	2.5 ± 0.3	4.8 ± 0.9	6.5 ± 2.6
<i>Topical morphine (patient 6 only)</i>			
C _{max} (nmol/L)	9.4	9.5	-
t _{max} (hr)	1	4	-
AUC _{0-tn} (nmol/l.hr)	56	82	-
Bioavailability % (AUC _{0-tn})	19.6	20.5	-

Values are mean ± SD except t_{max}, which is median (range)

6.4.3 Topical Morphine

Morphine, M3G and M6G were detected in the plasma of only one patient (Patient 6) after topical application of morphine sulphate, this patient had the largest ulcer (60 cm²) compared to an average of 12.8 cm² in the other five patients. Both morphine and M6G were first detected at one hour, were still detectable at 12 hours but were <LLQ by 24 hours. Morphine C_{max} was in the first post-treatment sample (one hour), while M6G C_{max} was at four hours. Trace amounts of M3G, below the LLQ, were detected between four and ten hours. Pharmacokinetic parameters for morphine and M6G are shown in Tables 6.2 & 6.3, with bioavailabilities of 19.6% and 20.5% respectively.

6.4.4 Adverse Events

During the topical application of morphine neither patients nor nursing staff reported any systemic or local adverse events. During subcutaneous administration of morphine one patient (Patient 2) reported drowsiness.

6.5 Discussion

Several different methods of assaying morphine have been reported in the literature including gas-liquid chromatography (Wasels et al. 1989; Brose et al. 1991), radioimmunoassay (Lee et al. 1991; Chapman et al. 1994; Chapman et al. 1995), thin layer chromatography, (Loh et al. 1973; Wang et al. 1986), gas chromatography particularly coupled to mass spectrometric detection (Leung 1994; Wasels and Belleville. 1994; Fryirs et al. 1997; Bogusz et al. 1996). This study used HPLC where morphine, M3G, and M6G were analysed using a previously reported method (Joel et al. 1988) and as described elsewhere (Pawula et al. 1993; Watson et al. 1996; Meng et al. 2000; Penson et al. 2000; Stuart-Harris et al. 2000; Penson et al. 2001; Penson et al. 2002).

The pharmacokinetics of morphine, M6G, and M3G have been described following oral, subcutaneous, and intravenous administration of morphine in healthy volunteers and patients. One volunteer study has described the pharmacokinetics of morphine hydrochloride in solution delivered from an occlusive reservoir applied to de-epithelialised skin (Westerling et al. 1994). The bioavailability of morphine from this route and formulation was 75%, with stable morphine concentrations maintained for 11 hours.

The aim of this study was to determine whether morphine sulphate in IntraSite gel was absorbed systemically when applied to ulcerated skin. In five of the six patients, morphine and its metabolites were undetectable, suggesting limited, if any, systemic absorption. In one

patient, who had the largest pressure sore, morphine and M6G were detected, with a bioavailability of 20%. The majority of cutaneous ulcers in clinical practice are smaller than that seen in patient 6 [Table 4.2], but it appears that if large ulcerated areas are treated topically, systemic absorption of morphine can occur. However, a bioavailability of 20% is unlikely to result in excessive systemic adverse effects given the relatively small daily dose of morphine applied topically with concentrations of less than 10 nmol/L across the study period, and the fact that most patients with advanced disease are also likely to be on oral opioids.

The subcutaneous infusion route was included to determine the relative bioavailability of topical morphine. The estimate of total plasma morphine clearance after subcutaneous infusion in this study is slightly lower than that previously derived in healthy subjects (Stuart-Harris et al. 2000) (1295 vs. 2125 mL/min), resulting in an increased AUC_{0-t} (356 vs. 205 nmol/L·hr). This was likely due to the effects of age and on-going disease in our study group.

IntraSite gel, a ready-mixed hydrogel containing water, propylene glycol, and carboxymethylcellulose, is widely used in the management of skin ulcers in the palliative care setting. When placed in contact with the wound, IntraSite gel absorbs excess exudates and produces a moist environment at the surface of the wound (Vernon 2000). These fluid handling properties may influence the pharmacokinetics of opioids when they are mixed with IntraSite gel and applied to skin ulcers. As hydrogels differ in the amounts of fluid they release or absorb (Thomas & Hay 1995), the degree of absorption of drugs from these gels may also vary.

Several opioids have been applied topically to ulcers, including diamorphine, morphine, and fentanyl. We have investigated the bioavailability of morphine, as it appears to be the most commonly used in published reports. The advantages of morphine over other opioids are that

it is widely available, is cheaper than most other opioid preparations, and is available in liquid form, which is easy to mix with a hydrophilic vehicle. Sampling of different parts of a morphine IntraSite gel mix prior to commencing the study, prepared as described in the methods of our study, showed that the mixture had a fairly homogeneous morphine concentration (variability in concentration <20% for four samples); others using HPLC have reported that homogeneity of the mixture was obtained after three minutes of mixing (Vernassiere et al. 2005). Furthermore the morphine/IntraSite gel mixture has been shown not to degrade over time, whereas diamorphine mixed with IntraSite gel showed some degradation to 6-monoacetylmorphine, and then morphine under the same conditions (see chapter 7).

6.6 Summary

When applied topically to ulcers in IntraSite gel, morphine is not absorbed except when there the ulcer has a large surface area. Reported analgesic effects after topical morphine are, therefore, likely to be mediated locally rather than systemically.

Chapter 7: Physical stability of opioids in IntraSite gel

Introduction

Stability is the capacity of a drug substance or drug product to remain within the established specifications to maintain its identity, strength, quality and purity throughout the re-test or expiration dating period (ICH 2003). The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a re-test period for the drug substance or a shelf life for the drug product and recommended storage conditions (ICH 2003). It is an essential factor of quality, safety and efficacy of a drug product. For example a drug may become less effective as it undergoes degradation or may yield toxic by-products that can be harmful to the patient.

Opioids commonly used in a palliative care setting include morphine, diamorphine, oxycodone and hydromorphone. Recent studies have suggested that if applied directly to painful ulcers that have a local analgesic effect. In many cases the opioids have been mixed with IntraSite gel (Chapter 2).

Morphine is the main pharmacologically active ingredient of opium extracted from the poppy *Papaver somniferum*. The chemical structure of morphine is that of a phenanthrene alkaloid, consisting of rings that are structurally rigid and would be chemically inactive were it not for the two hydroxyl groups at C3 and C6 (Resine & Pasternak 1996), the same two hydroxyl groups make it relatively water soluble and poorly lipid soluble. Morphine degrades in aqueous solution to

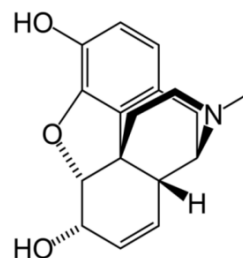


Figure 7.1 Chemical structure of morphine

pseudomorphine (a morphine dimer formed at the C7 position), morphine-N-oxide and possibly to apomorphine (Vermeire & Remon 1999).

Diamorphine is an opioid derivative synthesised from morphine by the addition of two acetyl groups at C3 and C6 making the molecule highly lipid soluble. It is generally considered to be a pro-drug without intrinsic activity (Inturrisi et al. 1984). Diamorphine hydrolyses to 6-monoacetylmorphine, and then to morphine, with potential morphine degradation products formed thereafter (Payne & Tempest 1988). Diamorphine has been widely used as the parenteral opioid of choice for cancer pain in the UK, but not elsewhere.

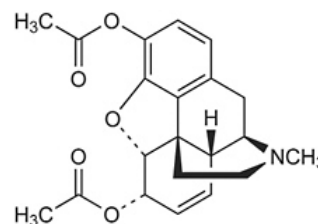


Figure 7.2 Chemical structure of diamorphine

Oxycodone is a semi-synthetic opioid derived from the opium alkaloid thebaine that has been in clinical practice since 1917. It is structurally related to morphine and widely used to manage cancer pain (Poyhia et al. 1993), although there is evidence to suggest oxycodone and morphine produce analgesia through different populations of opioid receptors (Smith et al. 2001). Oxycodone N-oxide and pseudooxycodone have been reported degradation products.

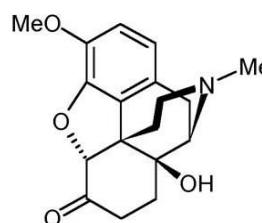


Figure 7.3 Chemical structure of oxycodone

Hydromorphone is a semi-synthetic derivative of

morphine with similar pharmacokinetic and pharmacodynamic properties that has been in clinical practice since the 1920s (Sarhill et al. 2001). It is a hydrogenated ketone of morphine, structurally the C6 hydroxyl group of morphine has been substituted with a carbonyl group and the double bond at the C7-8 position has been removed. Hydromorphone N-oxide, hydroxylated hydromorphone and pseudohydromorphone have been reported degradation products.

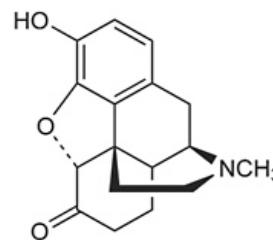


Figure 7.4 Chemical structure of hydromorphone

IntraSite gel is a colourless transparent aqueous gel, which contains 2.3% of a modified carboxymethylcellulose polymer together with propylene glycol (20%) as a humectant and preservative. When placed in contact with a wound, the dressing absorbs excess exudate and produces a moist environment at the surface of the wound, without causing tissue maceration (Vernon 2000).

IntraSite gel may be applied to many different types of wound, including leg ulcers, pressure sores, surgical wounds and extravasation injuries. It is of particular value in the treatment of dry, sloughy, or necrotic wounds, promoting rapid debridement by facilitating rehydration and autolysis of dead tissue. In the management of granulating wounds, IntraSite gel has been shown to prevent desiccation, and thus facilitates re-epithelialisation. Although there are no known contra-indications to the use of IntraSite as a topical wound dressing, the material is not ideally suited for application to wounds that are exuding very heavily.

7.2 Aims of physical stability studies

The aim of this study was to determine whether morphine, diamorphine, oxycodone and hydromorphone are stable when mixed with IntraSite gel at room temperature in the dark, at room temperature under normal day/night conditions and at 4°C in the dark, over a period of 28 days, and thereby determining the feasibility of extending expiration dates after mixing.

7.3 Materials

The pharmaceutical preparations of morphine sulphate and diamorphine hydrochloride were obtained from Arum Pharmaceuticals Ltd. Hydromorphone hydrochloride, pseudohydromorphone and hydromorphone-N-oxide (all dry powder) were obtained from Napp Pharmaceuticals Research Limited (Cambridge, UK). Morphine, morphine-N-oxide, pseudomorphine and naloxone were obtained from McFarlan Smith (Edinburgh, UK). Oxycodone hydrochloride was obtained as a dry powder, from Sigma Aldrich (Poole, Dorset, UK). This was used to determine the linearity of the standard curve. The pharmaceutical preparation of oxycodone (Oxynorm) was obtained from Napp Pharmaceuticals Research Limited (Cambridge, UK), for use in the both gel recovery and the stability studies. The formulation contained 10 mg active drug substance (oxycodone hydrochloride), citric acid monohydrate, sodium citrate, sodium chloride, sodium hydroxide, dilute hydrochloric acid and water for injection. Oxynorm was packaged in 1 mL ampoules. IntraSite gel was obtained from Smith & Nephew Healthcare Ltd (Hull, England). Sodium dodecyl sulphate (99% GC grade) and apomorphine were obtained from Sigma Aldrich (Poole, Dorset, UK). Sodium dihydrogen orthophosphate 1-hydrate (analar HPLC grade), acetonitrile (HPLC grade), orthophosphoric acid 85% (HPLC grade) and sodium hydroxide pellets (99%) were purchased from Merck (Enfield, UK) and 6-monoacetylmorphine (6-MAM) was provided by Dr Wynn Aherne, Institute of Cancer Research Sutton, Surrey, UK.

7.4 Methods

7.4.1 Analysis of opioids by HPLC

The studies were conducted using a Perkin Elmer series 200 HPLC system. The chromatographic conditions for the study were developed from a previously published method known to resolve morphine and its degradation products (Joel et al. 1988; Ribeiro et al. 2004). The mobile phase consisted of 10 mM sodium dihydrogen orthophosphate 1-hydrate and 0.8 mM sodium dodecyl sulphate with 25% acetonitrile (ACN). The pH of the solution was adjusted by drop wise addition of sodium hydroxide or orthophosphoric acid. The solution was then filtered using a Millipore solvent filtering system with 0.45 µm Millipore filter papers and a vacuum pump. Chromatic separation was achieved by using a Hyperclone HPLC 5 µM ODS (C18) column, 150 mm X 4.6 mm diameter. Flow rate and run time were set at 1.5 mL/min and 50 minutes respectively. Detection was by UV absorbance at 210 nm.

The pH of the buffer was adjusted to pH 2.0, 4.0, 6.0 or 8.0, and the system left to stabilise for two hours. The samples were then re-injected at each pH. Retention times and separation of the compounds were observed. The mixed solution of analytes spiked with compounds to act as possible internal standards (naltrexone or naloxone), was also used to optimise the ACN content in the mobile phase, and the flow rate.

Morphine and its known degradation products were used in establishing the run time for the method. As the study drugs are structurally related to morphine, it was expected that similar degradation products would be formed. The expected retention times for degradation products were estimated from the retention time relationship of morphine to morphine N-oxide and pseudomorphine. These data were used to determine the run time length.

7.4.2 Gel Homogeneity

Seven grams of IntraSite gel was expelled from the dosing pack into 25 mL sterile plastic containers. The respective opioid was then added and mixed for one minute using a sterile glass rod. As a standard comparison seven grams of phosphate buffer was weighed out on the balance into a 25 mL sterile plastic container. The opioid was then added and mixed by vortexing. Between 200-300 mg of gel was removed from the container using a sterile metal spatula and weighed. The sample was then diluted gravimetrically 1:10 with phosphate buffer. Ten samples from each gel were prepared in this manner. All were mixed by rotation for one hour at room temperature. Eight samples were obtained from the 'buffer' containers, with 200-300 mg of the sample being removed by Pasteur pipette then treated in the same way as the 'gel' samples.

All samples then underwent a second volumetric 1:10 dilution with phosphate buffer (as used in the mobile phase) in 1.5 mL eppendorf tubes. Duplicate second dilutions were made from all 10 of the gel samples. All samples were mixed for three seconds using the vortex mixer. Gel samples were also centrifuged at 4°C and 3000 rpm for five minutes before HPLC analysis. The final mobile phase consisted of 10 mM sodium dihydrogen phosphate, 0.8 mM sodium dodecyl sulphate (SDS) at pH 4.0, 71% buffer with 29% ACN. Mobile phase flow was 1.5 mL/min with a run time of 20 minutes.

7.4.3 Gel Stability

Triplicate preparations were made and stored at room temperature in day/night conditions (16 hour/8 hours respectively) on a laboratory bench out of direct sunlight but approximately 1.5 m from a fluorescent lamp that was illuminated between the hours of 9am and 5pm; in a fridge at 4°C in the dark and, at room temperature in the dark.

The study gels were removed from their place of storage. Using a sterile metal spatula 200-300 mg of gel was removed, placed into a labelled sterile plastic container and weighed. Gel samples were then treated as described in the recovery method. The gels were sampled on day 0 (baseline), 2, 4, 7, 10, 14, 21 and 28.

Samples containing drug and breakdown products were removed from the freezer and left to defrost at room temperature, before being mixed for three seconds with the vortex. These samples did not undergo any further dilution and were analysed at the beginning and end of the run. Standards were injected before the gel samples and quality control samples were inter-dispersed throughout the run. Extraction efficiency from the gel was calculated from the following:

$$\text{Extraction efficiency} = \frac{\text{Mean peak height of duplicate gel samples}}{\text{Mean peak height of all standard 'buffer' samples}} \times 100\%$$

Retention times were confirmed on the computer system. The software package then drew baselines for each peak, which were inspected and amended if necessary. A summary report of the retention time and peak heights was generated by the package and the data underwent further analysis using Microsoft Excel. Concentrations of the compounds of interest in both quality control and samples were determined from the known concentration and peak heights of the standards using the following formula: Response factor = $1/[\sum (\text{peak height}/\text{concentration})]/1$

A summary of the data were plotted and analysis of variance carried out using Minitab, controlling for storage condition, day, and sample replicate. As multiple ANOVAs were performed a p-value of 0.01 was taken as statistically significant.

7.5 Results

7.5.1 Stability of morphine in IntraSite gel

Chromatograms of mixed standards, morphine and diamorphine samples are shown in Figure 7.5. A total of 63 samples containing morphine sulphate were analysed. The mean extraction efficiency of morphine from gel was found to be almost 100%. No evidence of pseudomorphine or morphine-N-oxide was observed in any of the samples up to 28 days irrespective of the temperature and whether or not samples were exposed to light. The morphine concentration appeared to fall during the first 10 days of storage [Figure 7.6]. The fall appeared greatest in the samples exposed to light (30%), compared to samples kept in the dark (5%) and samples at 4°C (20%). After this initial period the measured morphine concentration remained unchanged to 28 days. As the fall in morphine concentration was not accompanied by a rise in known degradation products, poor sample mixing was a possible explanation. The study was therefore repeated employing more rigorous mixing and additional time points within the protocol.

Figure 7.5 Stability study No. 1: Chromatogram of mixed standard, morphine and diamorphine samples. Naltrexone used as internal standard

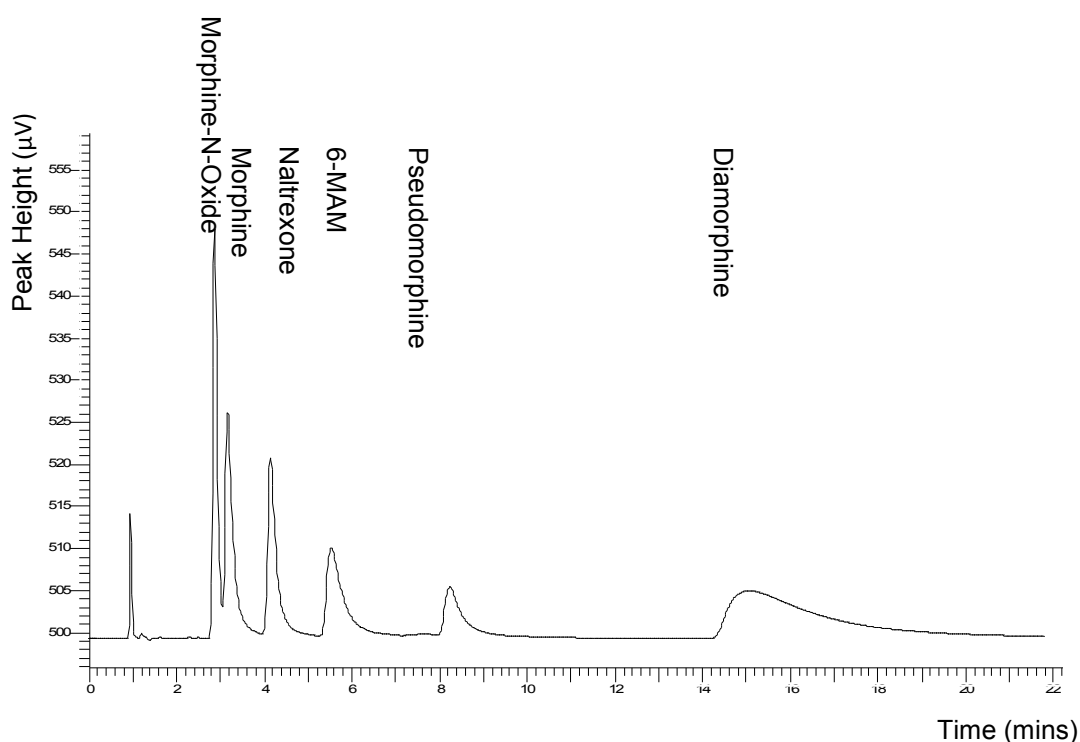
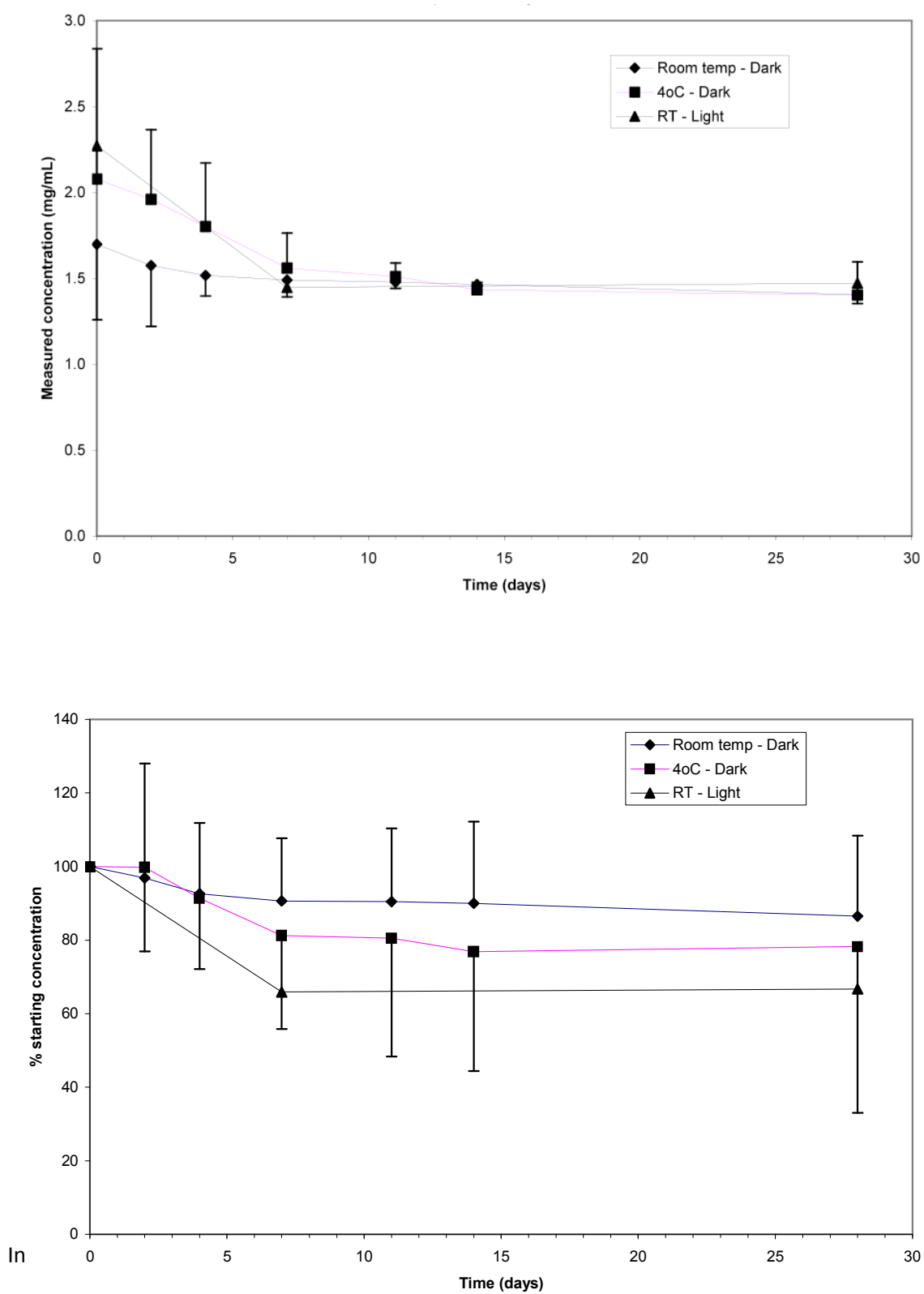


Figure 7.6 Stability study No. 1: Morphine stability in IntraSite gel at room temperature (dark and dark/light cycle) and at 4°C (Mean \pm SD).



the repeat study a total of 72 samples containing morphine sulphate were analysed. The repeat analysis confirmed no evidence of pseudomorphine or morphine-N-oxide in any of the samples up to 28 days irrespective of the temperature and whether or not samples were exposed to light [Figure 7.7]. The morphine concentration was again variable during the first five days of storage, after which recovered drug concentration stabilised [Figure 7.8]. Including all the data in an analysis on variance found no effect of storage conditions on morphine concentration ($p > 0.5$), but a significant time effect ($p = 0.001$). A similar analysis including data from day 8 onwards found no effect of storage time ($p = 0.250$), suggesting the time effect was due to variability in recovered morphine concentration across the first five days when mixing of the samples might have been incomplete. After this initial mixing period the measured morphine concentration remained unchanged to 28 days.

Figure 7.7 Stability study No. 2: Morphine stability at room temperature, day 28. Naltrexone used as internal standard

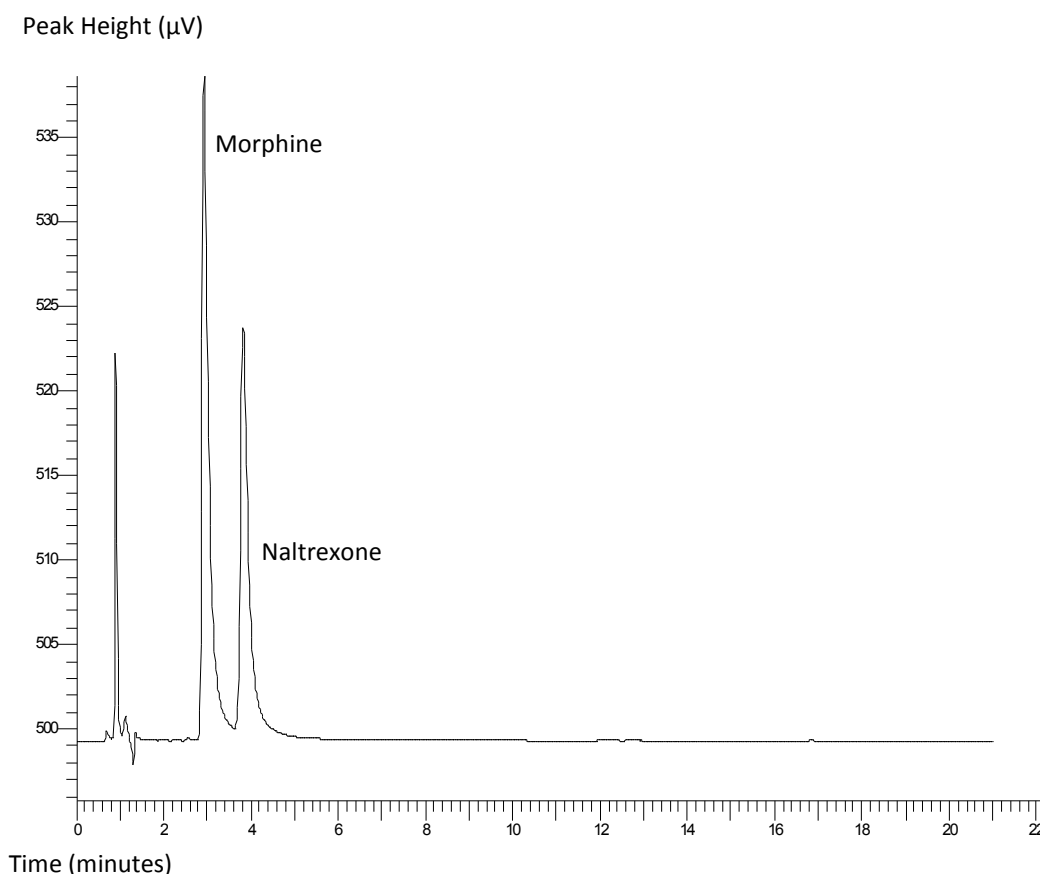
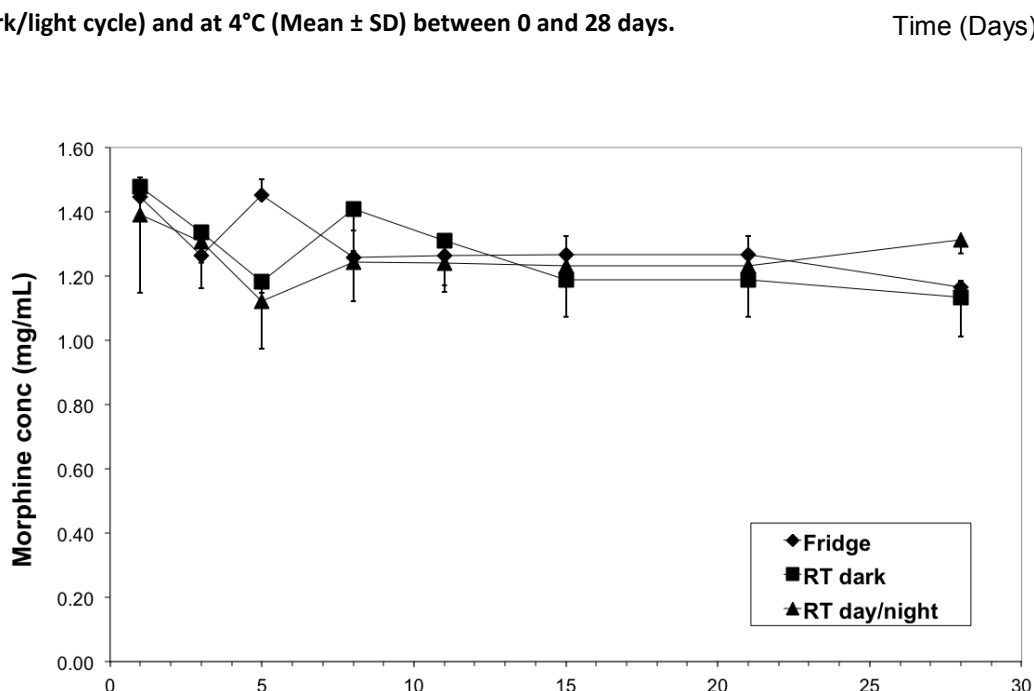


Figure 7.8 Stability study No. 2: Morphine stability in IntraSite gel at room temperature (dark and dark/light cycle) and at 4°C (Mean \pm SD) between 0 and 28 days.



7.5.2 Stability of diamorphine in IntraSite gel

The mean extraction efficiency of diamorphine from gel was found to almost 100%. Analysis of the 63 diamorphine samples showed that diamorphine hydrochloride was degraded to 6-MAM, and then to morphine. The rate and degree of degradation was related to the sample temperature. At room temperature the percentage 6-MAM (\pm SD) on day 7 was 7.1 (0.4) and on day 28, 30.2 (0.6), whereas at 4°C the percentages were 3.2 (3.5) and 4.5 (0.2) respectively [Figure 7.9]. No morphine degradation products were detected in any diamorphine samples. As with the first morphine stability samples there appeared to be a fall in diamorphine concentration which was smaller than that seen with morphine and could not be accounted for by the concentration of degradation products. It was not possible to determine whether this fall was directly related to diamorphine or whether the degradation to morphine subsequently lead to a fall in the latter's concentration giving the impression that less morphine was present than expected. The study was therefore repeated with more vigorous mixing and additional time points within the protocol.

Figure 7.9 Stability study No. 1: Stability of diamorphine hydrochloride in IntraSite gel stored at 4°C (A), at room temperature in the dark (B) and dark/light (C); (Mean + SD)

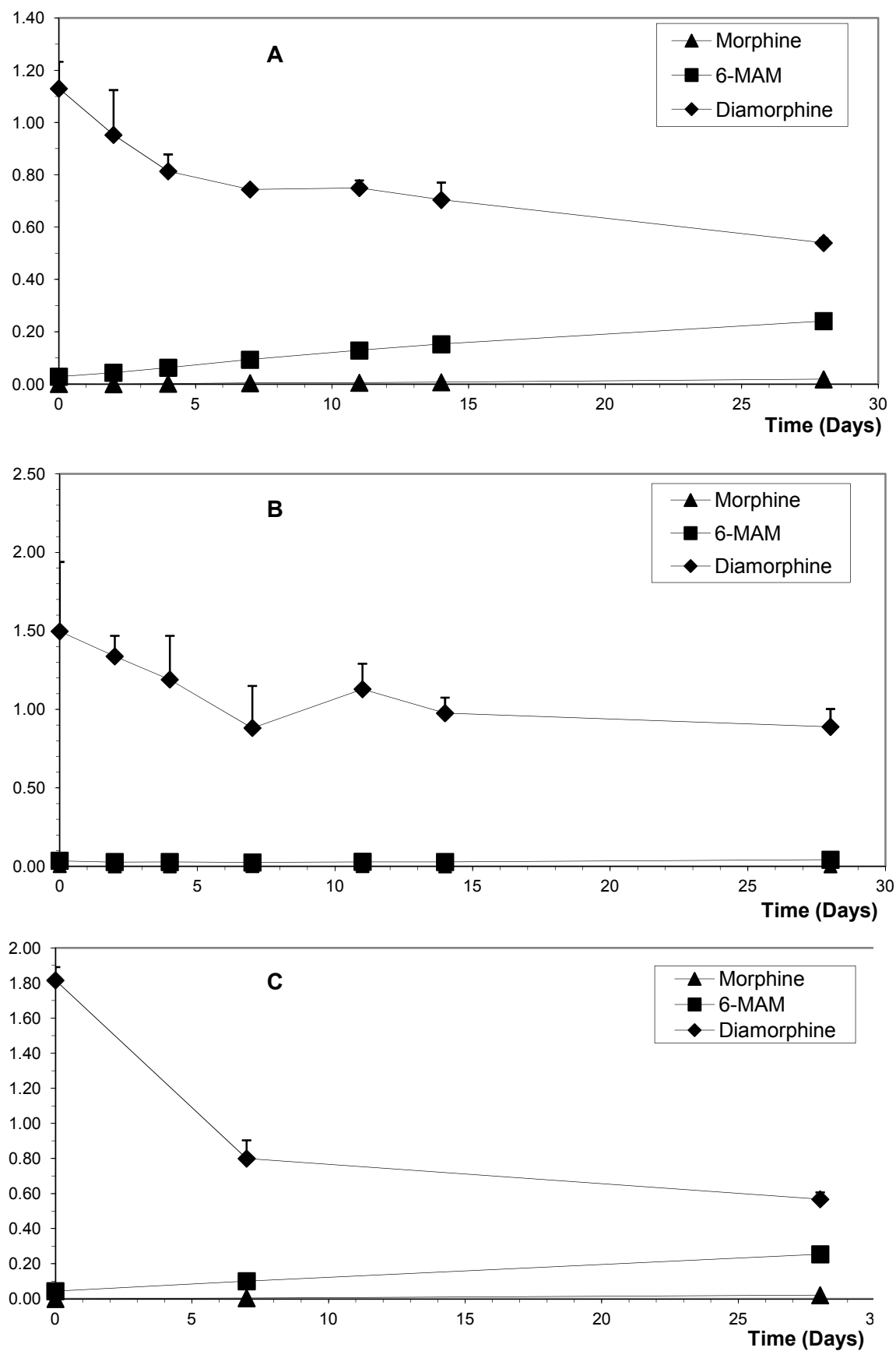


Figure 7.10 Stability study No. 2: Stability of diamorphine hydrochloride in IntraSite gel stored at 4°C at room temperature in the dark (B) and dark/light (C); (Mean \pm SD)

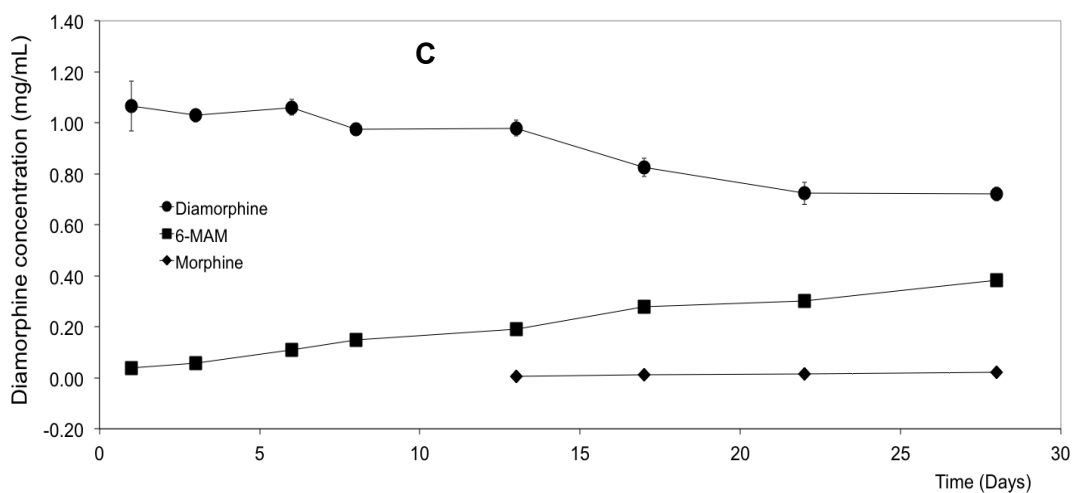
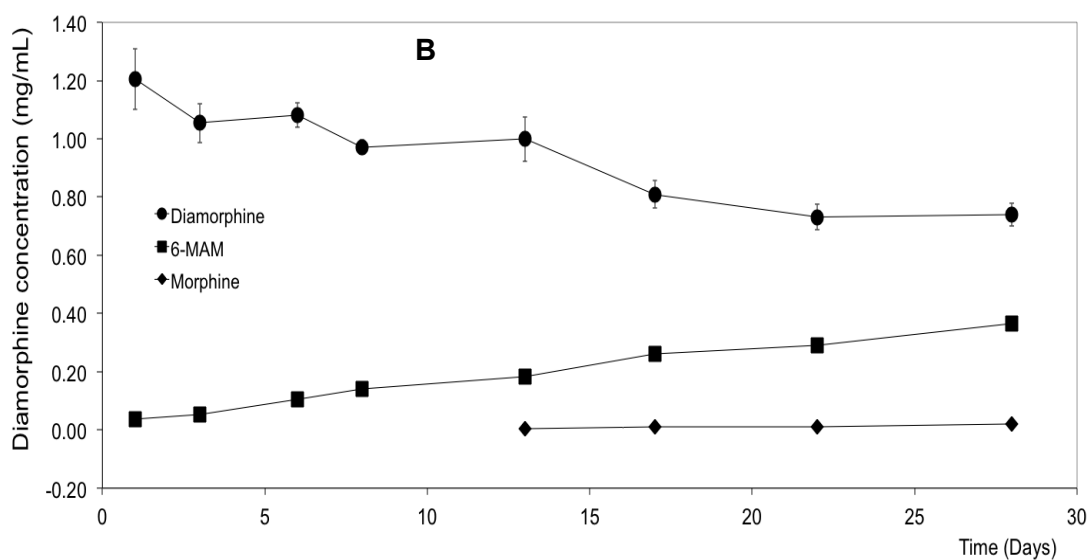
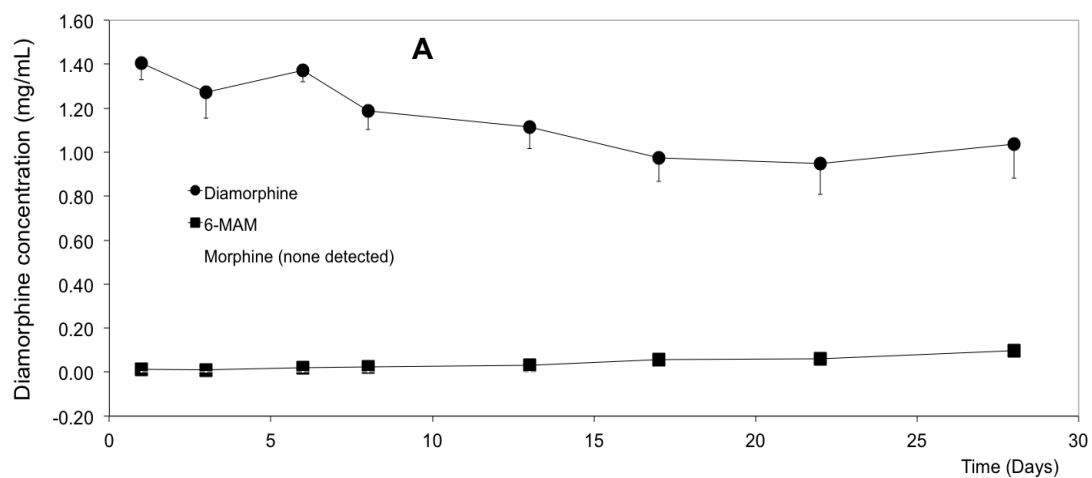
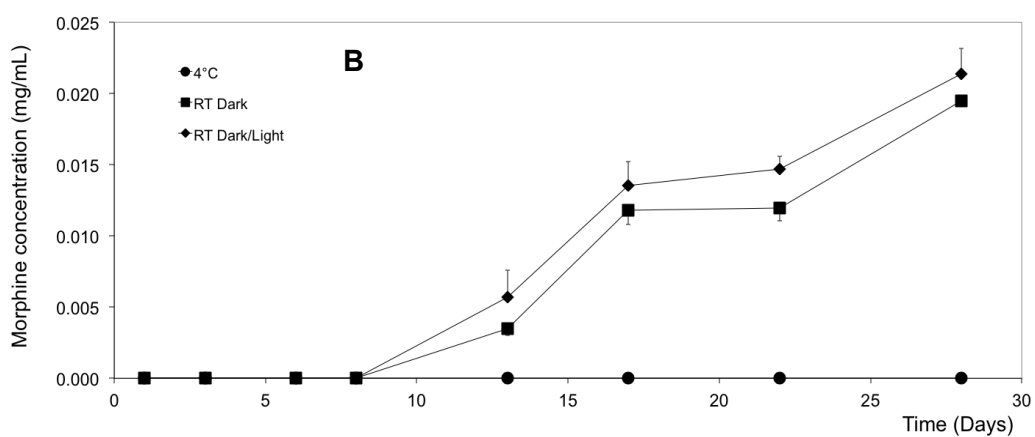
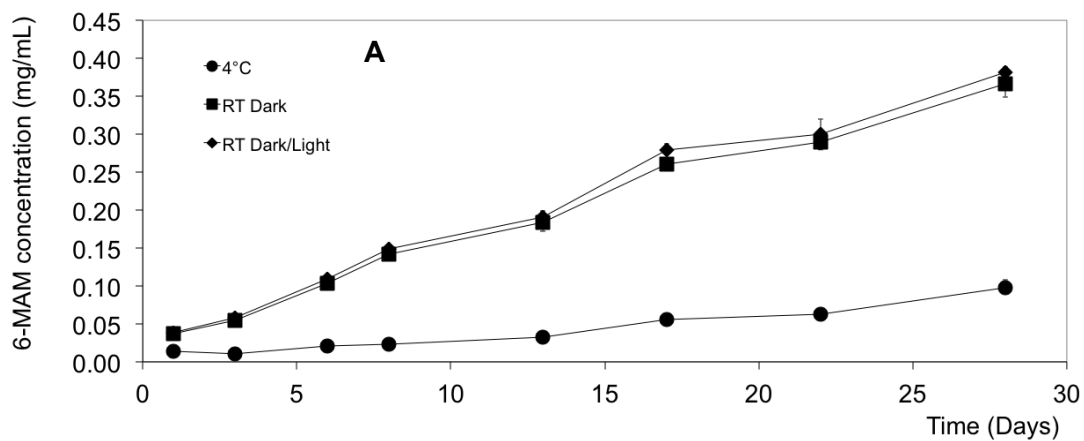
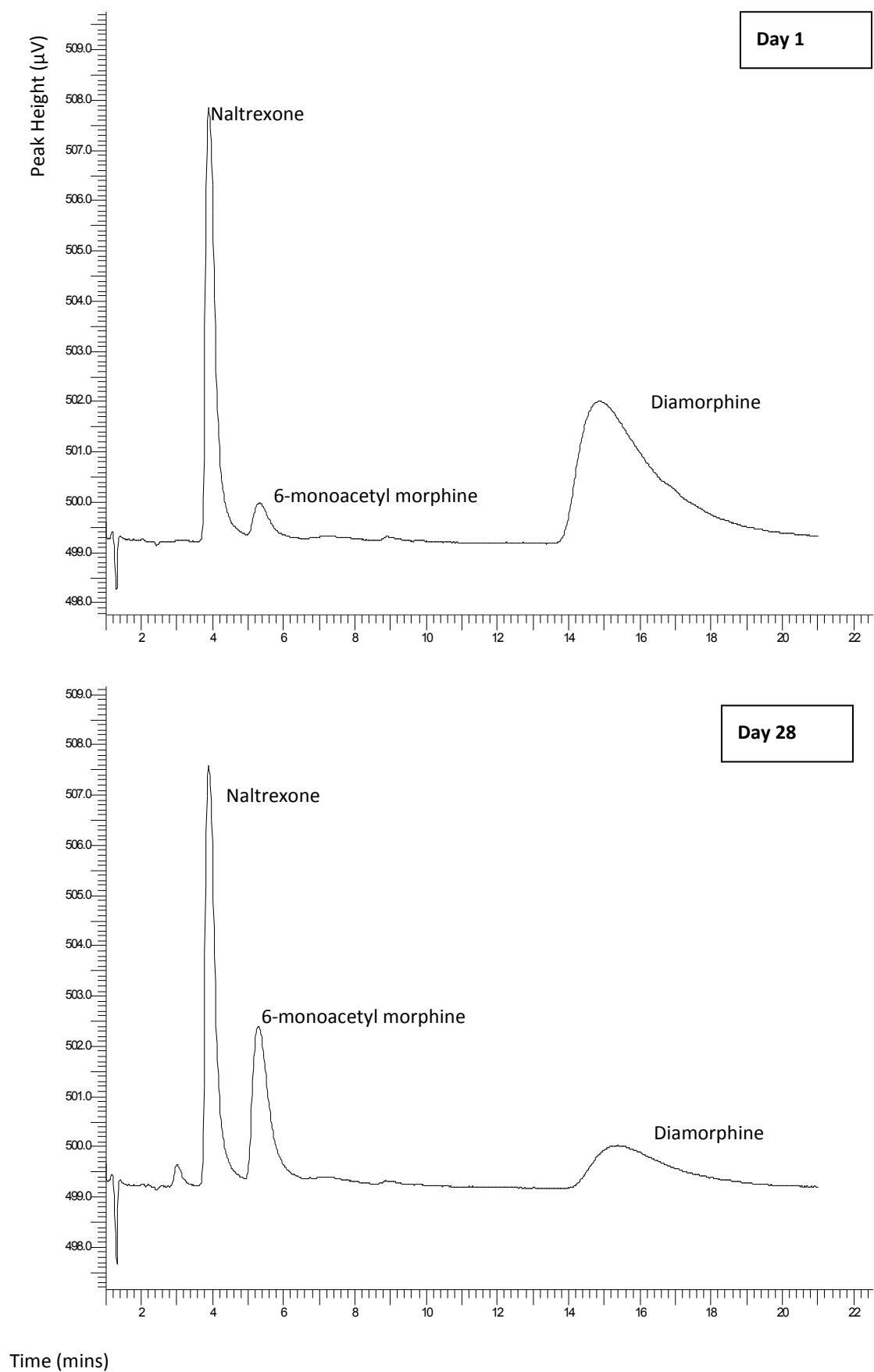


Figure 7.11 Stability study No. 2: The appearance of 6-MAM (A) and morphine (B) from diamorphine in IntraSite gel stored at different temperature and light conditions; (Mean \pm SD)



**Figure 7.12 Stability study No. 2: Diamorphine stability at room temperature (Days 1 and 28).
Naltrexone used as internal standard**



Analysis of the 72 diamorphine samples in the second stability study confirmed that diamorphine hydrochloride degraded first to 6-MAM, and then to morphine (ANOVA for storage time $p < 0.001$). The rate and degree of degradation was related to the storage conditions (ANOVA $p < 0.001$ for diamorphine, morphine and 6-MAM), with samples stored at room temperature showing a greater accumulation of 6-MAM with time than samples stored at 4°C (ANOVA $p < 0.001$) [Figures 7.10 & 7.11]. No morphine was detected in any sample stored at 4°C. Although the difference was small, recovered 6-MAM and morphine concentrations were consistently higher in samples stored at room temperature in the day/night light compared to dark (ANOVA $p = 0.001$ for 6-MAM and morphine). There was no difference in diamorphine concentration between these two storage conditions ($p = 0.11$). By day 28 this resulted in 6-MAM and morphine concentrations of 0.367 ± 0.018 mg/mL and 0.019 ± 0.001 mg/mL respectively in samples stored at room temperature in the dark and 0.381 ± 0.007 and 0.021 ± 0.002 mg/mL for those exposed to light. No further morphine degradation products were found [Figure 7.12].

7.5.3 Stability of oxycodone in IntraSite gel

Chromatograms of mixed standard are shown in Figures 7.13. The mean extraction efficiency of oxycodone from gel was found to be $96\% \pm 4.4\%$ and reproducibility across the 10 samples was 4.6%, representing intra-assay precision. Oxycodone concentrations appeared to show variability in all gels until day 7, after which time sample concentrations were more stable. Concentrations within the oxycodone gel were higher than expected. As in the other opioid studies starting concentrations of oxycodone varied between triplicate preparations stored under the same conditions and much of the variability occurred within the first few days [Figure 7.14]. There was no evidence of degradation products at the estimated times calculated from morphine degradation up to day 28 in any of the gels containing oxycodone, regardless of storage conditions. An unknown peak was detected at a position not expected of

a degradation product and appeared to increase with time as shown in Figure 7.15. This unknown peak was also apparent in quality control samples and standards but was not apparent in the 0 standard or buffer [Figure 7.16] suggesting that it was related to the drug.

An analysis of variance was performed to determine whether there was any significant change in the percentage concentration of the analytes from day 0 concentration between triplicate samples ($p < 0.001$), over time ($p = 0.042$) and across storage conditions ($p = 0.117$). A 2-way ANOVA was then performed to look at the effect of sample replicate and day for each condition. The variation in percentage of starting concentration over time was found to be significant in the gel stored at room temperature in the dark ($p = 0.002$) and suggested in the gel stored at 4°C in the dark ($p = 0.027$); there was no significant difference when the gel was stored at temperature in day/night condition ($p = 0.559$). There was a significant change in percentage concentration between the triplicate preparations stored at room temperature in the dark ($p < 0.001$) and room temperature in day/ night condition ($p < 0.001$), however no significant variation between the triplicate store at 4°C in the dark ($p = 0.08$).

7.5.4 Stability of hydromorphone in IntraSite gel

Hydromorphone concentration appeared to be variable up until day 4, irrespective of storage condition. After this time concentration across all of the gels became stable. Theoretical concentration of the drug in the gel was expected to be 1.25 mg/mL and the majority of samples were found to fall between 5% and 10% of this concentration. The mean extraction efficiency of hydromorphone from gel was found to be $92\% \pm 5.0\%$ with reproducibility across 10 samples of 5.5%, representing intra-assay precision. If this is taken into account it could be expected that the concentrations may be up to 8% higher, taking them close to the theoretical concentration. Data were plotted as measured hydromorphone concentration for each storage condition showing that much of the variation within the assay occurs within the first few days

[Figure 7.17].

Figure 7.13 Chromatogram showing separation of the analytes for the oxycodone assay. Naloxone used as internal standard

Peak Height (μV)

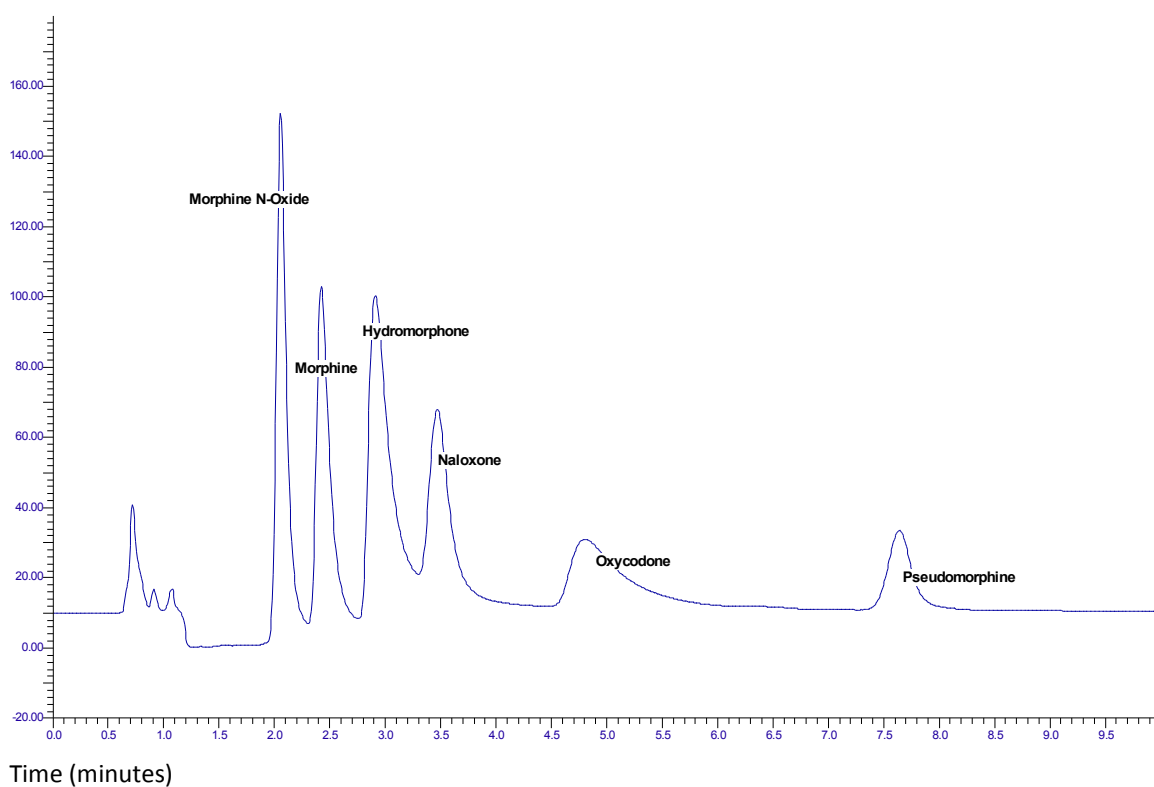


Figure 7.14 Graph of Oxycodone concentration over time in gels stored at each condition; (Mean \pm SD)

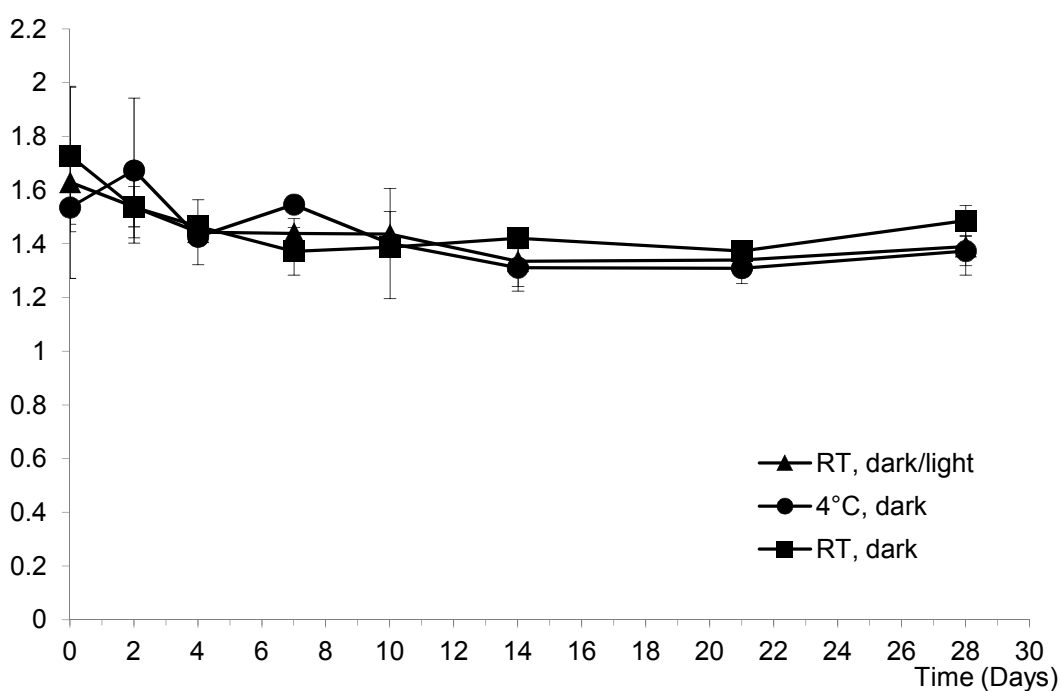
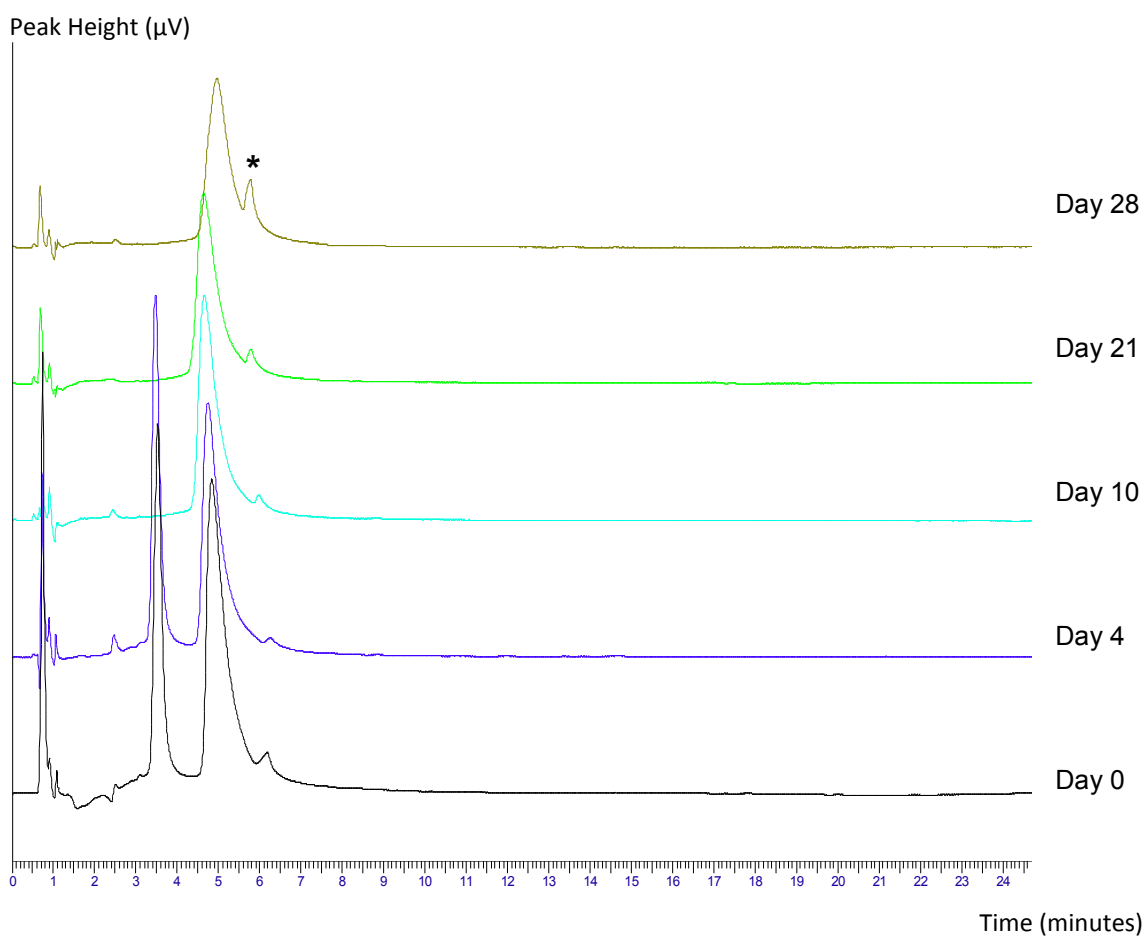
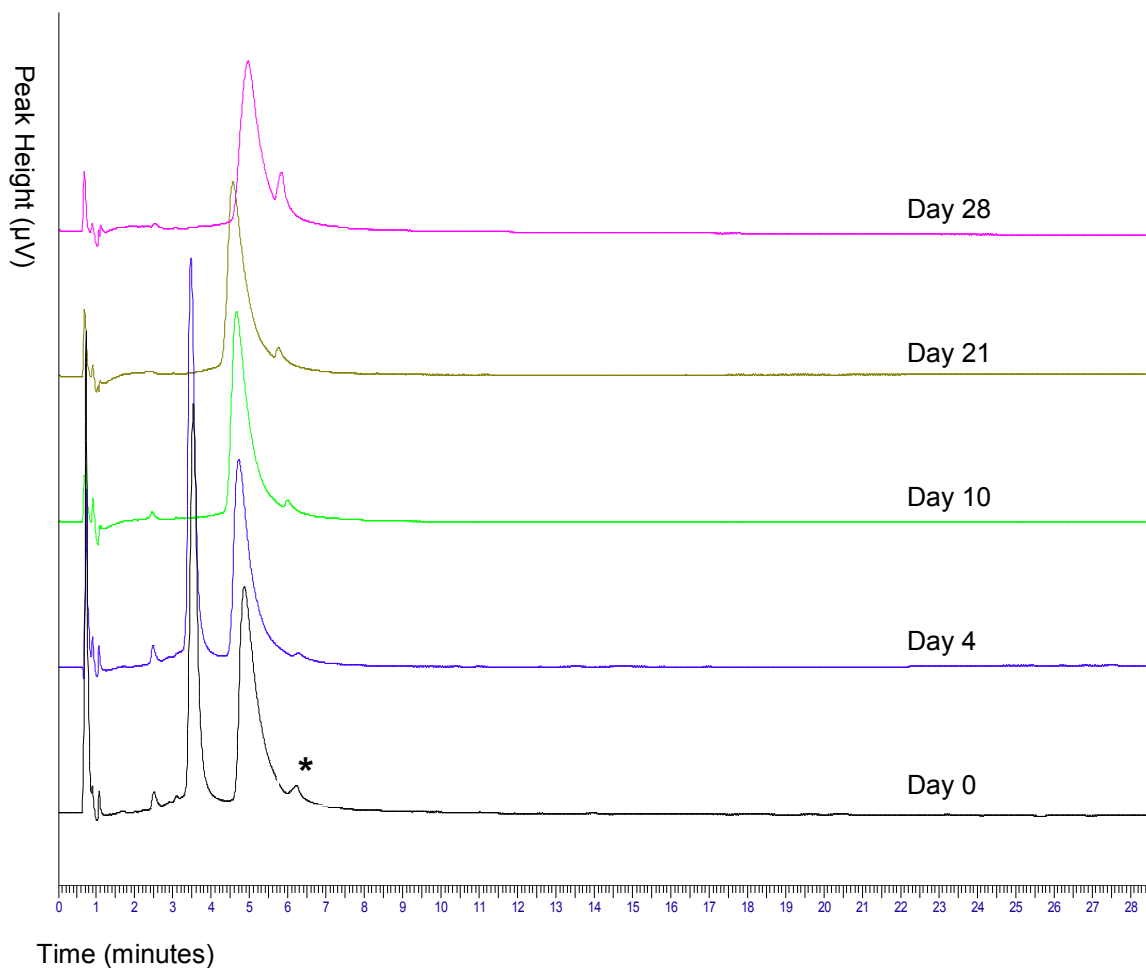


Figure 7.15 Chromatogram showing unknown peak in the oxycodone gel sample stored at room temperature in day/night conditions. (day 0 and day 4 contain internal standard, Naloxone at 3.5 minutes).



*Unknown peak

Figure 7.16 Chromatogram showing unknown peak in the oxycodone 1.2 mg/ml QC sample on day 0, 4, 10, 21 & 28 (day 0 and day 4 contain internal standard, Naloxone at 3.5 minutes).



* Unknown peak.

An analysis of variance was performed to determine whether there was any significant change in the percentage concentration of the analytes from day 0 concentration between triplicate samples ($p = 0.132$), over time ($p = 0.864$) and across storage conditions ($p = 0.396$) showing there was no significant change in percentage of day 0 concentration over the study period regardless of time, storage condition or triplicate sample.

No known degradation peaks were observed in any gel samples, on any day of the study regardless of storage condition. Figure 7.18 shows a sample of chromatograms from one triplicate stored at the day/ night condition at room temperature, on days 0, 4, 10, 21 and 28. While no known degradation products were seen, a peak of unknown origin was detected in all chromatograms [labelled in figure 7.18]. This peak appeared to increase with time with its peak area found to be approximately 3.3% of the hydromorphone peak area in gels from day 28. The peak was not detected in the Day 0 standard or phosphate buffer

Figure 7.17 Graph of hydromorphone concentration over time in all storage conditions.

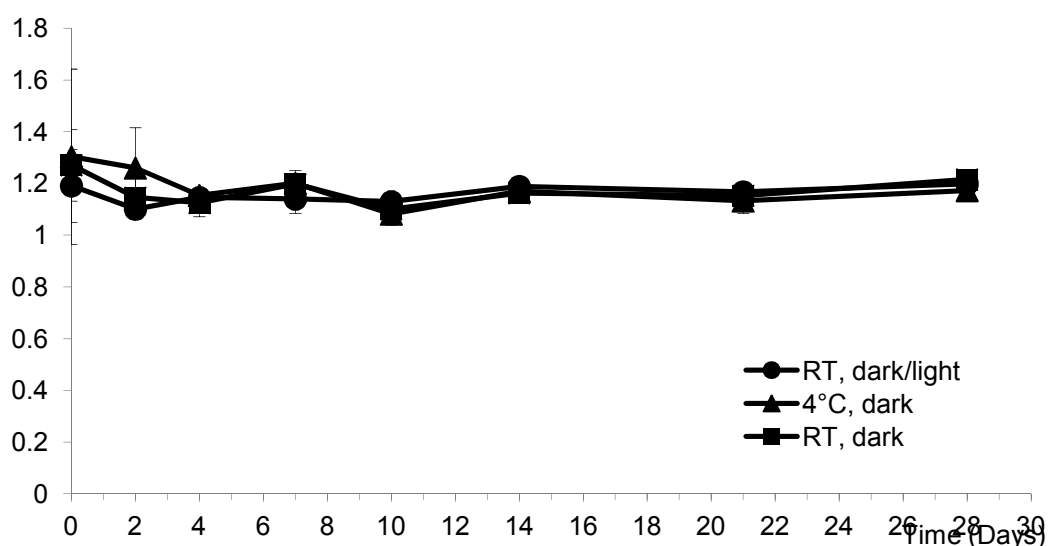
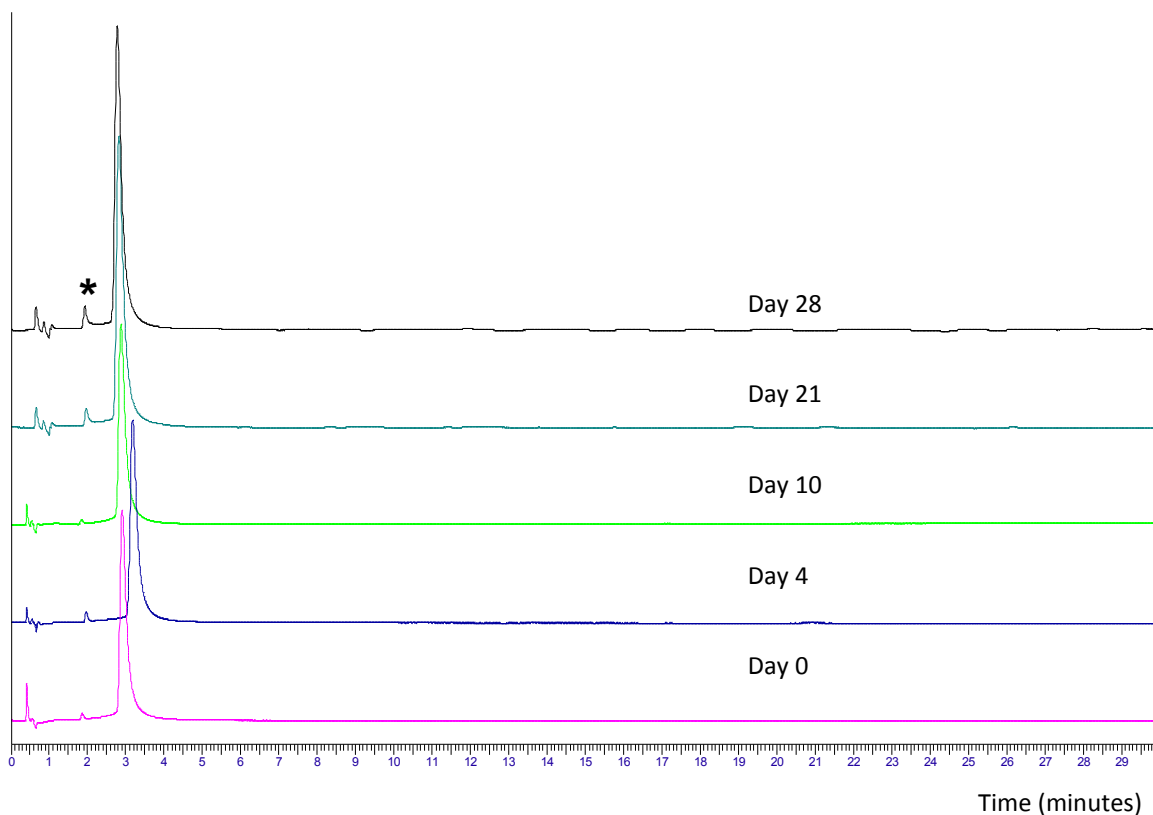


Figure 7.18 Chromatograms of hydromorphone 2.0 mg/ml standard on day 0, 4, 10, 21 and 28.

Peak height (μV)



* Unknown peak

7.6 Discussion

Stability testing is a routine procedure performed on drug substances and products. The design of the formal stability studies for the pharmaceutical product should be based on knowledge of the behaviour and properties of the active substance, and from stability studies on the active substance and on experience gained from pre-formulation studies and investigational pharmaceutical products (World Health Organization 2006).

Five types of stability are generally recognised:

- Chemical: Each active ingredient retains its chemical integrity and labelled potency, within the specified limits.

- Physical: The original physical properties, including appearance, palatability, uniformity, dissolution, and suspendability are retained.
- Microbiological: Sterility or resistance to microbial growth is retained according to the specified requirements. Antimicrobial agents that are present retain effectiveness within the specified limits.
- Therapeutic: The therapeutic effect remains unchanged.
- Toxicological: No significant increase in toxicity occurs.

This study addressed the chemical stability of the opioid-IntraSite gel mixtures.

Stability studies determine the drug substance or product's degradation as a result of exposure to a variety of conditions, such as temperature, humidity, light, orientation and packaging materials over an extended time frame. According to the ICH, significant change in drug product is a 5% change in the measured concentrations from its initial value, and any degradation product exceeding its acceptance criterion. Where the data show so little (< 5%, degradation), and variability the requested shelf life is granted (ICH 2003).

7.6.1 Morphine

The stability of morphine in aqueous solutions had been extensively investigated and it was generally accepted that oxygen from air, sunlight, UV irradiation, iron and organic impurities could promote the degradation of morphine (Yeh & Lach 1961; Vermeire & Remon 1999).

However several published reports have demonstrated that solutions of morphine sulphate for intravenous infusion appear to be relatively stable, irrespective of opioid concentration, storage temperature, storage container, whether or not they were protected by light and whether in combination with other drugs. (Vecchio et al.1988; Grassby & Hutchings 1993; Trissel et al. 2002a; Xu et al. 2002; Trissel et al. 2002b).

In our first study a fall was seen in morphine concentrations, which was not accompanied by a rise in the degradation products pseudomorphine or morphine-N-oxide. Possible explanations included precipitation or evaporation of morphine; poor mixing of the sample and that as molecules move with time they become more thoroughly mixed and concentrations become more uniform, and adherence of the drug to the containers. Poor mixing was assumed and although the second study showed some variation in morphine concentration during the initial five days, probably because of incomplete mixing, thereafter morphine appeared stable throughout the 28 days irrespective of the temperature and whether or not samples were exposed to light.

7.6.2 Diamorphine

Aqueous solutions of diamorphine are less stable than solutions of morphine. Degradation of diamorphine has been shown to occur at different concentrations, and at different temperatures and the percentage fall is directly related to initial concentration and accompanied by a corresponding increase in 6-MAM and to a lesser extent morphine (Poochikian & Craddock 1979; Poochikian et al. 1983; Barrett et al. 1992; Omar et al. 1989). Diamorphine is generally considered to be a pro-drug, which in vivo is rapidly hydrolysed by plasma cholinesterases and other blood and tissue esterases to active metabolites, although the presence of a novel mu receptor with which diamorphine, but not morphine, interact has been described (Rossi et al. 1996).

This study showed that the degradation of diamorphine occurred in vitro and was seven times greater at room temperature compared to 4°C. This would imply that diamorphine should be stored at low temperature and protected from light although the degradation products are active metabolites in themselves. Indeed if diamorphine is solely a pro-drug it appears illogical

to use it in this way. In addition to requiring metabolism to active metabolites it is not commonly available in all countries and more expensive i.e. assuming a 1.5 potency ratio between morphine and diamorphine (Scottish Intercollegiate Guidelines Network 2008) 10 mg diamorphine hydrochloride injection (£3.59) vs. 15 mg morphine sulphate injection 1ml (72p) (British National Formulary 2011).

7.6.3 Oxycodone

A number of assays have been developed for the analysis of oxycodone in plasma and in vitro when combined with other drugs (Kapil et al. 1992; Wright et al. 1998; Brogle et al. 1999; Gebauer et al. 2001; Turnbull et al. 2002; Hines & Pleasance 2009), but there are no stability data for oxycodone in IntraSite gel.

The data collated from this study found that the data were far more variable than those for the other opioids, a finding that may again be attributed to difficulties in achieving uniform mixing of the drug within the gel as occurred in the first morphine assays, or the finding might be related to the physico-chemical structure of the opioid interacting with the gel. The gradual stabilisation may have occurred secondary to a change in properties of the gel over time as observed during the period of the study or due to inadvertent mixing each time the gel was sampled. Results showed a statistically significant day effect on concentration in the gel stored at room temperature in the dark and suggested a day effect on concentration in the samples stored at 4°C in the dark.

An unknown peak was detected in all gels irrespective of storage condition and appeared to grow with time. As no known degradation products could be obtained to run with the samples, it was assumed that a degradation pattern of a similarly structured drug, morphine would occur (Gebauer 2001). Estimations of the expected retention times were based on the pattern

seen in morphine degradation, however the peak did not occur at any of these estimated times. This peak was also detected in quality control and standard samples that were stored at -40°C and therefore unlikely to have degraded.

A previous study (Gebauer 2001) showed oxycodone to be stable for up to a year when stored under refrigeration in pre-packaged syringes. The large variability within this study, coupled with significant changes in concentration of drug over a 28 day study period suggest that further work is required before comparison with other studies can be made.

7.6.4 Hydromorphone

The stability of hydromorphone has been demonstrated in several published studies either alone, with other drugs and in a variety of delivery systems (Walker et al. 1991; Hildebrand et al. 2001; Trissel et al. 2002c; Nassr et al. 2003; Khondkar et al. 2010).

In this study hydromorphone was found to be stable, with no significant change in starting concentration regardless of storage condition, time or replicate. A small peak of unknown origin, not eluting at a position expected for known degradation products of hydromorphone was however, detected at a retention time of two minutes. This peak was present in all gel samples regardless of storage condition and appeared to increase in size over time, with a peak area on day 28 of approximately 3.3% of hydromorphone peak area. It is pertinent that this peak was also present in the quality control and standard samples. These samples were made up on day one and stored in aliquots at -40°C so is unlikely that this peak results from an unknown degradation product. Hydromorphone concentration over the study stabilised at a concentration lower than the expected theoretical concentration of 1.25 mg/mL. This finding is not explained by the formation of degradation products but may be accounted for by slightly reduced extraction efficiency from the gel.

7.7 Summary

The results of this study suggest that morphine and hydromorphone remain stable when mixed with IntraSite gel for up to 28 days, whereas diamorphine degrades to 6-MAM and then to morphine, which then remains stable. The results for oxycodone were too variable, perhaps due to contamination, to recommend its use without further testing. The results are limited to the methods employed in the study and do not offer information on the stability of the same opioids in different concentrations, prepared using different salts or formulations, prepared in a different way, at different temperatures or stored for longer periods of time.

Chapter 8: Microbiological stability of morphine in

IntraSite gel

8.1 Introduction

A sterility test is a test that critically assesses whether a sterilised pharmaceutical product is free from contaminating microorganisms. The term sterility means no surviving organisms whatsoever; there are no degrees of sterility and no level of contamination that is considered negligible, insignificant or acceptable (Denyer & Hodges 2004).

When preparing drug mixtures a number of potential sources may be problematic including water (e.g. gram-negative groups: pseudomonas, xanthamonas, flavobacterium) and air (e.g. mould spores: penicillium, aspergillus, bacterial spores: bacillus species, yeasts). The risk of contamination is more likely in non sterile than in sterile products and in multiple use formulations compared to single unit dose systems. A number of steps may be helpful to prevent contamination to the formulation during storage including the use of suitably designing the containers (ideally single dose), adhering to proper storage conditions and adding an antimicrobial substance as preservative.

IntraSite gel is an amorphous hydrogel consisting of water (> 60%), glycol (10-30%) and absorbent polymer (< 10%), developed for the debridement of necrotic tissue and the absorption of slough and exudate; IntraSite gel is available as a single use 'Applipak' capsule thus reducing the risk of contamination [Figure 8.1]. The capsule is sterilised by steam and advice from the manufactures, Smith & Nephew Healthcare Ltd, is that it should be stored in a cool dry place when it will have a three-year shelf life; once opened the capsule should be stored in a cool dry place and used within one week. HPLC methods have determined that morphine-IntraSite gel mixtures may be physically stable for up to 28 days (Chapter 7);

however it has not been shown whether the mixture is microbiologically stable for the same period of time.

Figure 8.1 IntraSite Gel Capsule (Smith & Nephew Healthcare Ltd) containing 8 g of gel



8.2 Aim of microbiological stability study

The aim of this study was to determine the microbiological stability of pre-prepared mixtures of 10 mg morphine-IntraSite gel at room temperature in the dark, at room temperature under normal day/night conditions and at 4°C in the dark, over a period of 28 days, and thereby determining the feasibility of extending expiration dates after mixing.

8.3 Methods

The morphine mixture was prepared using morphine sulphate injection BP 10 mg/mL (Celltech Pharmaceuticals, Berkshire, UK) and IntraSite gel 8 g (Smith & Nephew Healthcare Ltd, Middlesex, UK). The preparation took place in a clean area of the laboratory without use of special equipment, such as a laminar airflow hood, and the conditions were not dissimilar from a typical palliative care ward environment. Using a sterile syringe and needle 1 mL morphine was injected directly in to the IntraSite container and mixed by shaking; 50 samples were prepared, each one using a separate needle and syringe. Five samples were taken at random

for baseline microbiological analysis (Day 0) and the remaining 45 were randomly divided equally between three test storage conditions. Each of the three samples sets were randomly labelled 1 to 15 and then stored in their respective conditions (room temperature in the dark, room temperature under normal day/night conditions and 4°C in the dark) and sent for microbiological analysis in groups of five; day 7 (samples 1-5), day 14 (samples 6-10) and day 28 (samples 11-15).

Microbiological analysis was undertaken at the Royal London Hospital Microbiology Department, where in order to isolate specific microbial contaminants a number of processes were used to detect the presence of:

1. Non-specific organisms: Blood, MacConkey incubated at 37°C in CO₂ for 48hrs;
2. Acinetobacter, coliforms or Pseudomonas: Blood and MacConkey agar at 37°C in CO₂ for 48hrs;
3. Staphalococcus Aureus or Group A Streptococci: CNA agar at 37°C in CO₂ for 48 hrs;
4. MRSA: MRSA selective media at 30°C for 18 hours;
5. Aspergillus and other fungi or yeasts: Sabouraud's media with chloramphenicol.

Once the samples were received each IntraSite gel capsule and appropriate culture plates were identified with a unique bar coded number. A 1 µL sterile disposable loop was inserted into the IntraSite gel capsule and the material inoculated onto a Blood agar, MacConkey agar, and a Sabouraud's agar plate. The inoculum was spread with a sterile loop for discrete colonies. Plates were then incubated at 37°C in CO₂ in accordance with established laboratory procedures. Culture plates were examined at 24 hours and if no growth obtained were re-incubated for a further five days before discarding. Any growth was identified and the results recorded on a Winpath a Laboratory Information Management System.

8.4 Results

Of the 50 samples sent for microbiological analysis no growth was identified in any of the samples at days 0, 7 and 14. One colony of *Corynebacterium coyleae* was identified in one of the five gel samples stored at room temperature in both light and dark conditions and tested after 28 days storage, but not in any of the other storage conditions [Table 8.1].

Table 8.1 Results of microbiological analysis of morphine sulphate mixed with IntraSite gel at stored in three storage conditions: samples tested at Days 0, 7, 14 and 28

Day	Fridge	Room temperature (dark)	Room temperature (light/dark)
0	No Growth	No Growth	No Growth
7	No Growth	No Growth	No Growth
14	No Growth	No Growth	No Growth
28	No Growth	No Growth	One colony of <i>Corynebacterium coyleae</i>

8.5 Discussion

Sterility is an important component of any preparation intended for contact with broken skin, particularly when the threat of infection exists, as in the case in chronic cutaneous wounds. A sterility test should assess whether a product is free from contaminating microorganisms by incubation of either the whole or a part of that product with a nutrient medium. (Denyer & Hodges 2004). The results of this study suggest that the mixed samples prepared in a ward type environment remained microbiologically stable for up to 14 days in any of the three storage conditions, and up to 28 days if stored in the fridge or at room temperature in the dark. A colony of *Corynebacterium coyleae* was isolated in one of the gel samples stored at room temperature for 28 days in both light and dark suggesting if samples are to be stored for more than 14 days prior to use, this should not be at room temperature.

Corynebacterium coyleae was first described in isolates from clinical samples in 1997 and named after Marie Coyle for her contribution to the clinical microbiology of Coryneform bacteria (Funke et al. 1997). *Corynebacterium coyleae* are Gram-positive rod-shaped aerobic, non-motile bacteria and one of the largest genera within the Actinobacteria that currently embraces over 50 species, most of which are innocuous (Collins et al 2004); the most notable human infection is diphtheria, caused by *Corynebacterium diphtheriae* [Table 8.2].

Corynebacterium coyleae is an environmental organism and although generally considered to be harmless has been isolated in clinical samples associated with sepsis (Fernández-Natal et al. 2008).

Table 8.2 Select *Corynebacterium* species associated with disease (Rogers et al. 2011)

Organism	Associated disease
<i>C. diphtheriae</i> (toxogenic)	Respiratory diphtheria
	Cutaneous diphtheria
	Pharyngitis
<i>C. diphtheriae</i> (non-toxogenic)	Endocarditis
<i>C. ulcerans</i>	Respiratory diphtheria
	Zoonotic infections
<i>C. jeikeium</i>	Septicaemia, endocarditis
	Wound infections
	Catheter/shunt infections
<i>C. amycolatum</i>	Septicaemia
	Respiratory tract infections
	Urinary tract infections
	Wound infections
<i>C. urealyticum</i>	Catheter/shunt infections
	Urinary tract infections (pyelonephritis, cystitis)
	Wound infections
<i>C. pseudotuberculosis</i>	Septicaemia, endocarditis
	Abscess formation
	Lymphadenitis
	Ulcerative lymphangitis

Hydrogel dressings are most commonly supplied as an amorphous, cohesive topical application that can take up the shape of a wound. They are designed to provide and maintain a moist wound environment and by increasing moisture content, hydrogels have the ability to help cleans and debride necrotic tissue (Jones & Milton 2000). Nine amorphous hydrogel preparations are listed in the British National Formulary, five of which, including IntraSite gel, contain propylene glycol (British National Formulary 2011). Propylene glycol is a chemically inert molecule that acts as a humectant preventing the gel from drying out and improving its handling, however it may also help preserve the sterility of the dressing due to its bacteriostatic properties. Research undertaken by Smith and Nephew reported the effect of IntraSite Gel and Purilon gel on microbial proliferation. The two gels were each inoculated with *Staphylococcus aureus*, *Pseudomonas aeruginosa* or *Candida albicans* and, in contrast to Purilon, IntraSite Gel showed bacteriostatic and fungistatic activity in-vitro against all three different test organisms (Harrow 2011.). The same bacteriostatic features had already been identified in other areas of experimental and clinical practice (Bazzicalupo et al. 1951; Bahn & Michalsen 1961). The presence of propylene glycol in IntraSite gel may have therefore contributed to the relative stability of samples stored in the fridge and at room temperature in the dark

In considering the results one should determine whether the absence of contamination in other samples was a consequence of using unsuitable media or that the sampling process was not random and bias was introduced into the methodology. A wide spectrum of microbiological testing was used and randomisation of samples took place in three stages of the preparation process, which will have improved the reliability of the results. The next step would be to adopt the procedures laid down by the European Pharmacopoeia that provides details on sample size, specific media employed, sampling, control samples and re-testing (European Pharmacopoeia 2002).

The microbiological stability considered in combination with the physical stability results presented in Chapter 7 suggest that morphine IntraSite gel mixtures can be prepared in advance, but carefully stored, increasing the convenience of this treatment option, particularly for patients with painful cutaneous ulcers managed at home. If the sterility of the product is to be ensured, the sterilisation, aseptic filling and closing operations must be adequately validated. In order to improve the microbiological stability of the morphine IntraSite mixture and ensure a longer shelf life, a sterilisation process should occur after the constituents have been mixed. Sterilisation processes may involve elevated temperature, reactive gas, irradiation, or through a microorganism proof filter (Soper & Davies 1990). IntraSite gel is sterilised with elevated temperature using steam whereas morphine is irradiated, furthermore heat sterilisation of morphine is not recommended. The sterilisation process is thus a compromise between achieving optimum antimicrobial activity and maintaining product stability, hence if the mixture were to be sterilised, selecting the method is important as there is a potential risk of product damage that could result in reduced therapeutic efficacy and stability, requiring a new set of efficacy and stability studies in this new formulation.

8.6 Summary

The results of this study suggest that a mixture of morphine and IntraSite gel prepared using aseptic technique in a ward type environment remains microbiologically stable for up to 14 days in any of the three storage conditions, and up to 28 days if stored in the fridge or at room temperature in the dark. The results are limited to the methods employed in the study and do not offer information on the stability of the same opioid prepared using different methods or for longer periods of time.

Chapter 9: Opioids applied topically to painful cutaneous ulcers: results of introducing a titration protocol into clinical practice

9.1 Introduction

Cutaneous ulcers are a heterogeneous problem that can vary in aetiology, pathophysiology and chronicity (Maida et al. 2008). In many cases healing of these wounds is not possible and a palliative approach is required to help manage the multiplicity of problems associated with them.

Palliative care is an approach to improve quality of life through impeccable assessment of symptoms within a holistic framework. Any given individual will have their own disease course, consequences and coping strategies, the only way to ensure appropriate and adequate management is to adopt an individualised approach. This principle applies equally to pharmacological and non-pharmacological treatment modalities.

Several pharmacological strategies may be appropriate for the management of pain in patients with cancer based on an assessment of the individual patient characteristics, co-morbidities, and other treatments that may influence drug absorption, pharmacokinetics, and pharmacodynamics. For example during the titration of background pain using opioids, supplemental doses of opioids are advised, the dose of which is based on the patient's background dose (Hanks et al. 2001). However when background pain is controlled but patients experience breakthrough pain, the optimum dose of analgesic can be difficult to predict and therefore most safely determined by titration (Davies et al 2009; Caraceni et al. 2012). Given the heterogeneity of cutaneous ulcers and the variability of the pain that they are associated with (Krasner 1995) the same principle of analgesic titration may apply to the use of

topically applied opioids.

There has been interest in the use of topically applied opioids to cutaneous wounds in our hospice. In addition to a few publications, one of the nursing staff undertook a review on the treatment of painful ulcers as part of her palliative care degree following which the clinical team agreed to introduce a clinical protocol for the management of ulcers in order that the problem was assessed and managed in a systematic manner. This management protocol was introduced into hospice clinical practice in May 2007 with the agreement of the hospice clinical governance committee and the in-patient unit manager. Central to this protocol was the titration of topically applied opioids (usually morphine) based on the patient's assessment of ulcer pain and their decision as to whether or not a change in opioid dose was required.

9.2 Aims of case note review

The aim of this study was to review the titration protocol introduced into clinical practice in May 2007 to determine whether or not topical morphine application was effective, if so at what dose(s), whether there was relationship between the effective topical morphine dose and the patient's background medication, and the length of time required for the patient to determine an effective dose of topical opioid.

9.3 Methods

A retrospective case note review of patients admitted between 1st April 2009 and 31st March 2010 and assessed for topical opioid administration was undertaken. Hospice IT staff identified patients admitted in the study period using the hospice patient database (iCare), administrative staff identified the location of the clinical notes and I then retrieved and reviewed all the identified clinical notes in order to review and record the relevant data.

The titration protocol introduced two years previously was standard nursing practice on the hospice inpatient unit and staff were trained when it was first introduced; new staff since May 2007 were trained on the use of the protocol as part of their induction. In accordance with the titration protocol the painful ulcer was first assessed in terms of grade, surface area, aetiology, pain severity and suitability for a once daily dressing using IntraSite gel; the effectiveness of previous analgesia (if prescribed) for the ulcer was also documented [Figures 9.1 & 9.2].

When the dressing change was due, the ulcer was first exposed by removing the previous dressing and then thoroughly cleaned with saline to remove any exudate, debris, slough or contaminants. Morphine mixed with IntraSite gel was applied directly to the wound, after which the ulcer was covered with a Tegaderm dressing. An aseptic non-touch technique was used throughout the procedure to prevent the introduction of potentially pathogenic micro-organisms into the wound. Education, training and assessment in the aseptic technique are provided to all persons undertaking such procedures and the technique is standardised across the organisation.

Following the initial assessment the protocol was initiated. The starting dose of morphine was 5 mg; 10 mg was offered if the patient rated the pain as either severe or excruciating using a VRS. If during the titration process the morphine-IntraSite mixture became too fluid to be reliably retained in the wound, switching to diamorphine was considered, which as a powder could be dissolved in small volumes of normal saline. The starting dose of diamorphine was based on the previous dose for morphine assuming a relative potency of 1.5 (i.e. 45 mg morphine was equivalent to 30 mg diamorphine) based on recommended oral opioid conversion charts (Scottish Intercollegiate Guidelines Network 2008).

Pain intensity was reviewed daily at the dressing change, when patients were asked to rate the pain from the ulcer in the last 24 hours since the last dressing change using a five point verbal rating scale (no pain, mild, moderate, severe or excruciating). Patients were then asked whether they wished the dose of analgesia to increase, decrease, or remain unchanged; increases or decreases were made in 5 to 10 mg steps depending on pain severity. Titration was deemed successful when patients no longer requested changes in their dose of morphine and the dose remained stable for at least two consecutive days.

The data from the titration protocol clinical documentation sheet was entered onto a data collection form together with information from the patient's medication chart to confirm the doses of morphine prescribed, and over what period of time. To minimise omissions all other sections of the clinical notes used during the admission by either nurses or doctors were reviewed to cross check the information obtained from both the wound assessment and the medication charts. Missing data were noted during the collation process and identified during the analyses. Data were entered on a Microsoft Excel database and means compared using parametric or non-parametric, as appropriate. In the statistical analysis $p < 0.05$ was deemed to be statistically significant.

Formal ethical approval was not sought, however the case note review was agreed by the hospice clinical governance working group and the hospice Caldicott Guardian, a senior clinician within the Hospice responsible for protecting the confidentiality of patient and service-user information and enabling appropriate information-sharing (Department of Health 2010).

Figure 9.1 Topical opioid treatment protocol: front sheet with instructions for clinical staff when considering topical opioid treatment for painful cutaneous ulcers

Titration protocol for topical opioids

Introduction

There has been some interest on the use of morphine topically for painful ulcers. The potential advantage is that by producing a local analgesic effect systemic medication can be reduced and/or avoided and there is less chance of systemic adverse effects occurring.

The most commonly applied opioid is morphine although there are also reports of diamorphine, fentanyl, oxycodone, hydromorphone and methadone. Most studies have been case reports in adults although some controlled studies in adults and small case series in children have been published. The majority of patients described have presented with painful non-malignant ulcers, in particular pressure sores.

The reason for introducing this protocol is to avoid inconsistency when using topical opioids

Method

- The ulcer will be assessed and its size measured
- The wound be assessed for the suitability of using IntraSite gel, Metronidazole gel, or KY jelly)
- The opioid should be mixed with a known measured amount of carrier (e.g. intrasite, and then the area of the wound covered
- The opioid of choice will be morphine sulphate injection at a starting dose of 5mg
- If the patient requires breakthrough medication for the wound this should be documents and administered in the usual way
- The topical analgesia will be routinely reviewed at each dressing change
- If the patient chooses for the analgesic to be increased this should be done in 5mg steps
- If the patient chooses for the analgesic to be decreased this should be done in 5mg steps
- If the dose of opioid is such that the mixture becomes too fluid and difficult to retain on the wound, diamorphine will be used as an alternative opioid. The starting dose of diamorphine will be based on the previous dose for morphine using the IPU opioid conversion tables

Figure 9.2 Topical opioid treatment protocol: clinical documentation sheet to record ulcer characteristics, pain severity, analgesia effectiveness and whether patient chooses to change opioid dose

Patients Name: _____

Nature of ulcer (please tick)

☐ Pressure ulcer ☐ Malignant ulcer

☐ Other (please specify ie arterial ulcer, venous ulcer)

Surface area to be treated (cm²) _____

Assessment

On average how intense has the pain been from the ulcer since the previous dressing change?

☐ No pain ☐ Mild ☐ Moderate ☐ Severe ☐ Excruciating

How effective are the painkillers: Ineffective ☐ Partially effective ☐ Completely effective ☐

Day 1: Starting morphine dose _____

On average how intense has the pain been from the ulcer since the previous dressing change?

☐ No pain ☐ Mild ☐ Moderate ☐ Severe ☐ Excruciating

Would you like the dose of painkiller to: Decrease ☐ Remain the same ☐ Increase ☐

Day 2: Morphine dose _____

On average how intense has the pain been from the ulcer since the previous dressing change?

☐ No pain ☐ Mild ☐ Moderate ☐ Severe ☐ Excruciating

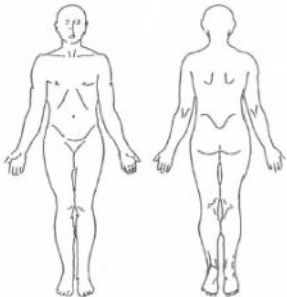
Would you like the dose of painkiller to: Decrease ☐ Remain the same ☐ Increase ☐

Day 3: Morphine dose _____

On average how intense has the pain been from the ulcer since the previous dressing change?

☐ No pain ☐ Mild ☐ Moderate ☐ Severe ☐ Excruciating

Would you like the dose of painkiller to: Decrease ☐ Remain the same ☐ Increase ☐



9.4 Results

During the survey period 175 patients were admitted to the hospice, the average age (range) age was 70.3 years (28-97) and 89 (51%) were female. The notes of all patients were reviewed and there were no missing data. Of the 175 patients admitted, 55 patients (32%) had painful ulcers and were considered by the clinical staff for topical opioid analgesia; 21 of the 55 patients (38%) were excluded from the protocol because of having either necrotic ulcers (15) or infection (6). The remaining 34 patients participated in the protocol; 20 (59%) were male [Table 9.1], the average age (range) of patients enrolled was 69 years (38-89). Seven patients withdrew during the titration protocol because of deterioration (3 patients), confusion (3) or pain worsening (1). Of the 27 evaluable patients 14 (52%) were male and their average age (range) was 69 years (38-89) [Table 9.2]. All but one ulcer was of benign aetiology and the mean (\pm SD) surface area was 13 (9) cm². All but four patients were taking opioid analgesia; the average (\pm SD) morphine equivalent daily dose was 121 (179) mg.

All patients reported that they experienced background pain from their cutaneous ulcers that was mild (2 ulcers), moderate (11), severe (9) or excruciating (5). Seventeen ulcers had transient exacerbations of pain that were described as severe (6) or excruciating (11) and usually brought about by movement (12), friction (8), dressing change (7) or a combination of these factors

Six patients (22%) reported that they had been prescribed analgesics specifically for the pain caused by the cutaneous ulcer, namely morphine (3 patients), paracetamol (3), oxycodone (2), NSAIDs (2) all on 'as required basis'; three patients were prescribed two analgesics. Patients reported the effectiveness of their analgesia as completely effective (1 patient), partially effective (4) and ineffective (2).

Table 9.1 Characteristics of all patients commenced on the titration protocol for topically applied opioid

Patient	Sex	Age	Regular analgesia	Rescue analgesia	Ulcer site	Surface area (cm ²)	Ulcer aetiology
1	M	82	Methadone 2mg bd	Morphine 2.5mg PO	Heel	6	Pressure
2	M	68	Diamorphine 30mg/24 SC	Diamorphine 5mg/24 SC	Hip	8	Pressure
3	M	75	Morphine 30mg/24 SC	Diamorphine 2.5mg SC	Sacral	3.5	Pressure
4	F	67	Fentanyl TTS 75mcg/h	Morphine 50mg PO	Sacral	15	Pressure
5	M	77	Alfentanil 1mg/24 SC	Alfentanil 0.5mg SC	Sacral	45	Pressure
6	F	83	Co-codamol 30/500 2 qds	Paracetamol 1g PO	Hip	12	Pressure
7	F	72	Buprenorphine TDS 20mcg/h	Morphine 2.5mg PO	Heel	5	Pressure
8	M	89	Morphine 10mg/24h SC	Morphine 1.25mg SC	Sacral	6	Pressure
9	M	69	Morphine 20mg bd	Morphine 10mg PO	Sacral	6	Pressure
10	F	69	Nil	Morphine 2.5mg PO	Sacral	4.25	Pressure
11	F	38	Oxycodone 30mg/24h SC	Oxycodone 10mg SC	Sacral	8.5	Pressure
12	F	78	Morphine 10mg 4hrly	Morphine 10mg PO	Sacral	23	Pressure
13	F	50	Diamorphine 10mg/24 SC	Diamorphine 2.5mg SC	Sacral	21	Pressure
14	F	61	Oxycodone 20mg/24 SC	Oxycodone 10mg SC	Sacral	35	Pressure
15	M	72	Morphine 10mg/24 SC	Morphine 10mg SC	Sacral	29	Pressure
16	M	52	Diamorphine 250mg/24 SC	Diamorphine 50mg SC	Sacral	24	Pressure
17	F	81	Fentanyl TTS 25mcg/h	Morphine 5mg PO	Sacral	12	Pressure
18	M	52	Fentanyl TTS 37mcg/h	Morphine 25mg PO	Sacral	14	Pressure
19	F	81	Morphine 60mg/24 PO	Morphine 10mg PO	Sacral	3	Pressure

Patient	Sex	Age	Regular analgesia	Rescue analgesia	Ulcer site	Surface area (cm ²)	Ulcer aetiology
20	M	65	Nil	Nil	Sacral	7	Pressure
21	F	76	Oxycodone 120mg/24h SC	Oxycodone 50mg PO	Sacral	5	Pressure
22	M	45	Fentanyl TTS 125mcg/h	Morphine 60mg PO	Sacral	15	Pressure
23	F	85	Fentanyl TTS 37mcg/h	Morphine 15mg PO	Sacral	9	Pressure
24	M	75	Nil	Co-codamol 8/500 PO	Sacral	25	Pressure
25	M	65	Alfentanil 6mg/24 SC	Alfentanil 1mg SC	Sacral	30	Pressure
26	M	67	Fentanyl TTS 75mcg/h	Oxycodone 15mg PO	Sacral	6	Pressure
27	M	68	Alfentanil 5mg/24h SC	Morphine 10mg PO	Sacral	7	Pressure
28	F	61	Alfentanil 0.5mg/24h SC	Alfentanil 0.1mg SC	Sacral	14	Pressure
29	M	73	Fentanyl TTS 125mcg/h	Morphine 60mg PO	Abdomen	14	Tumour
30	M	78	Morphine 10mg/24 SC	Morphine 10mg SC	Sacral	4	Pressure
31	F	64	Diamorphine 10mg/24 SC	Morphine 10mg PO	Sacral	5	Pressure
32	M	80	Alfentanil 2mg/24 SC	Alfentanil 0.5mg SC	Sacral	24	Pressure
33	M	58	Morphine 10mg/24 SC	Morphine 10mg PO	Hip	13	Pressure
34	M	76	Nil	Morphine 2.5mg PO	Sacral	20	Pressure

Table 9.2 Changes on pre and post titration morphine dose				
Patient	Starting dose (mg)	Final dose (mg)	Days to final dose	Days at final dose
1	5	15	3	5
2	5	10	2	5
3	5	10	2	4
4	5	10	2	3
5	5	5	Withdrawn	
6	5	15	3	6
7	10	10	1	9
8	5	10	2	4
9	10	10	Withdrawn	
10	5	5	1	16
11	5	25	29	12
12	5	10	2	19
13	5	5	1	6
14	5	10	2	12
15	5	10	2	6
16	5	5	Withdrawn	
17	5	10	3	14
18	5	5	Withdrawn	
19	10	20	11	12
20	5	15	3	4
21	5	5	Withdrawn	
22	10	10	1	8
23	5	10	2	8
24	5	10	Withdrawn	
25	5	5	1	7
26	10	10	1	4
27	5	10	2	13
28	5	20	4	6
29	5	20	6	11
30	5	5	1	4
31	5	10	2	5
32	5	10	Withdrawn	
33	10	60	14	8
34	5	15	3	5

Patients who had determined an effective dose of topical morphine were titrated for a median (mean \pm SD) of 9 (11 \pm 8) days (range 4-40). All but one patient were titrated solely with topical morphine; patient 33 was switched to diamorphine during the titration as the gel become too fluid. The median (mean \pm SD) successful morphine equivalent dose achieved through titration was 10 mg (12.2 \pm 9.8) range 5-60 mg [Figure 9.3] and the median (mean \pm SD) time to titration was 2 days (4 \pm 5.9). If the three patients with the longest titration periods are removed (for reasons see later) the median (mean \pm SD) successful morphine dose achieved through titration was 10 mg (10 \pm 4.1) and the time to titration was 2 days (2.2 \pm 1.2). There was no simple relationship between the successfully titrated dose of topical morphine and the dose of background opioid, (correlation coefficient $r = -0.07$, $t = 0.35$, $p > 0.05$), [Figure 9.4].

Following titration, efficacy was rated as partial in 14 patients and complete in 13 patients. Topically applied morphine appeared to have a beneficial effect on both background and transitory pain. Converting the VRS to a five point NRS where 0 = no pain and 4 = excruciating pain, the median (mean \pm SD) pre-treatment background pain was 3 (2.6 \pm 0.8) compared to 0 (0.4 \pm 0.6) post treatment (Wilcoxon signed rank test $p < 0.01$). Of the 17 patients experiencing transitory pain the median (mean \pm SD) pre and post-treatment pain scores were 4 (3.7 \pm 0.5) and 1 (1.2 \pm 0.8) respectively ($p < 0.01$) [Figure 9.5]. Three patients no longer reported transitory pain, 14 reported improvements in the frequency of episodes (3 patients), pain severity (5) or both (6).

Figure 9.3 Review of clinical protocol for the titration of topically applied opioids: Morphine doses that patients deemed successful

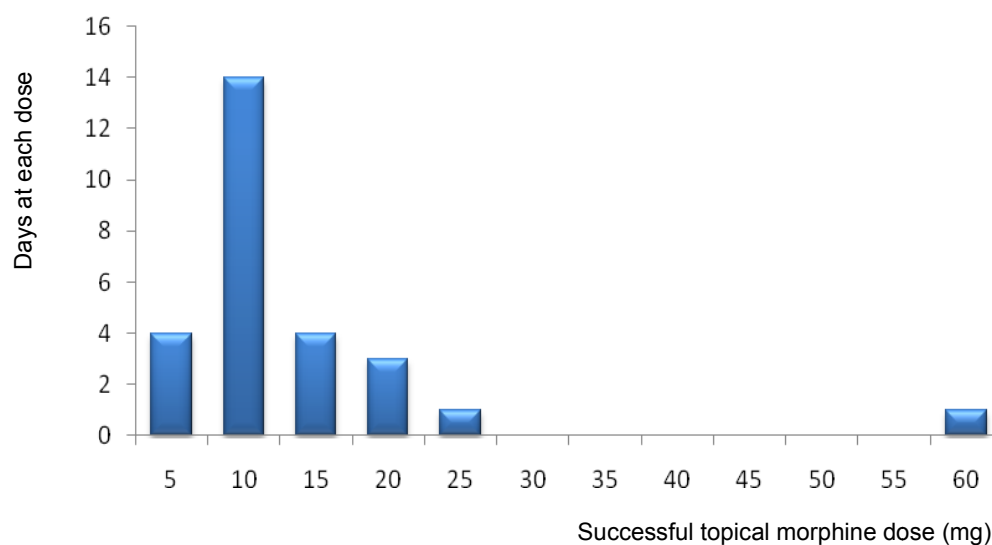


Figure 9.4 Review of clinical protocol for the titration of topically applied opioids: Relationship between successfully titrated topical morphine dose and patients' regularly scheduled opioid analgesia ($r = -0.07$, $p > 0.05$)

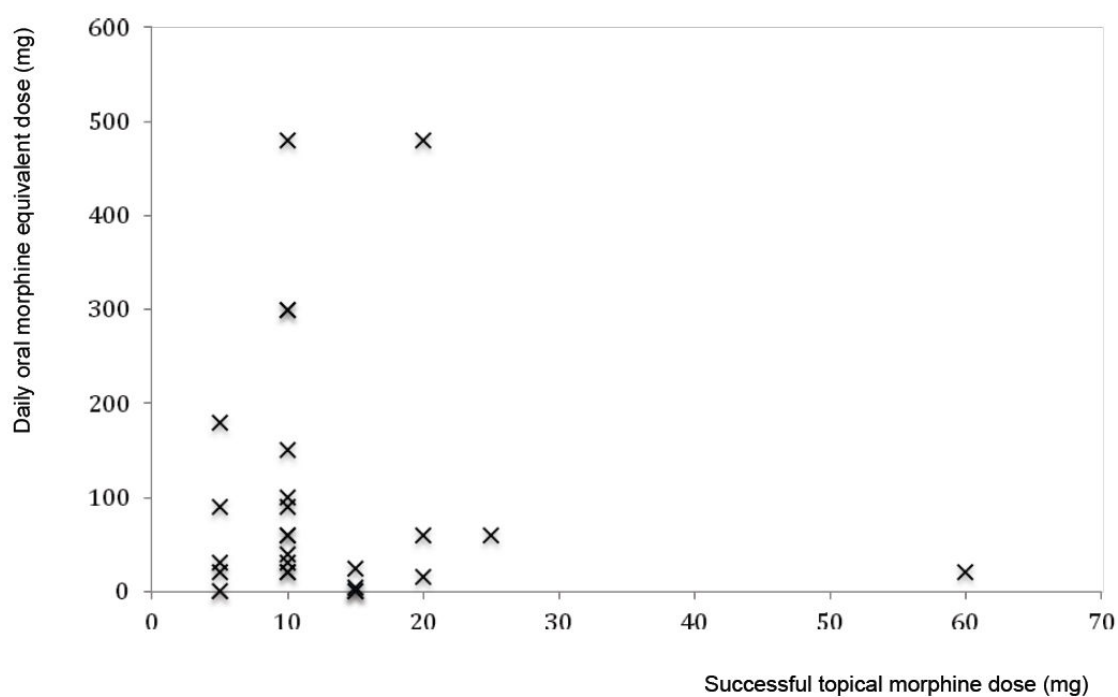
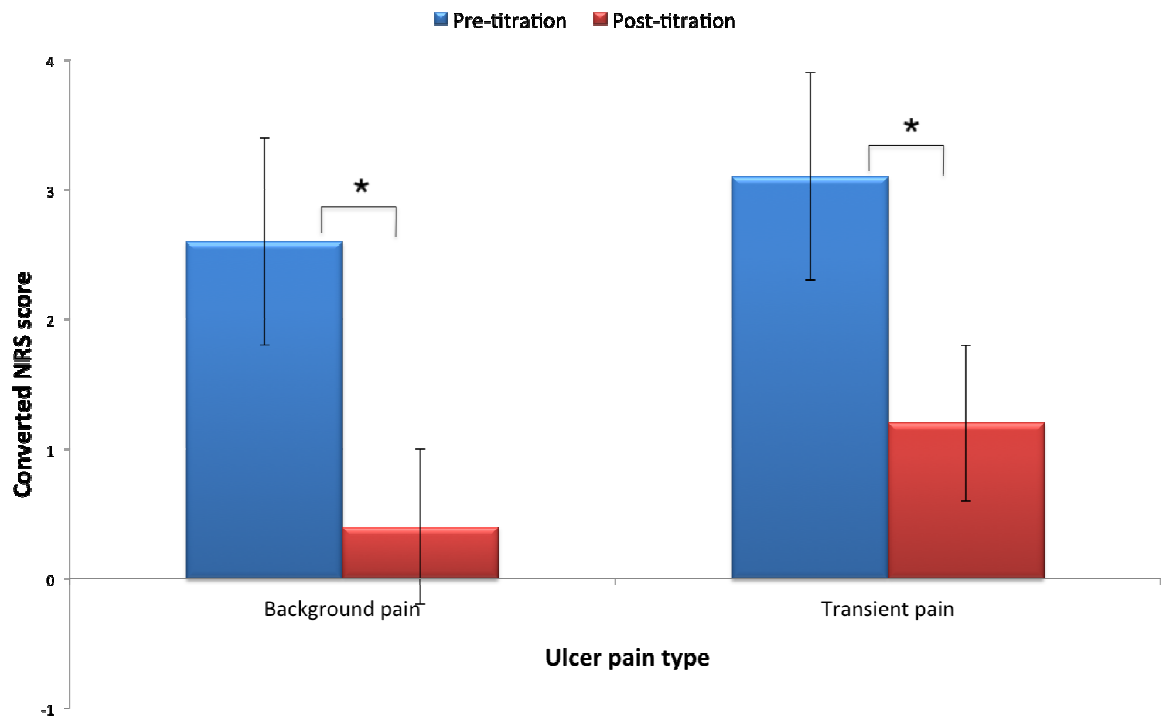


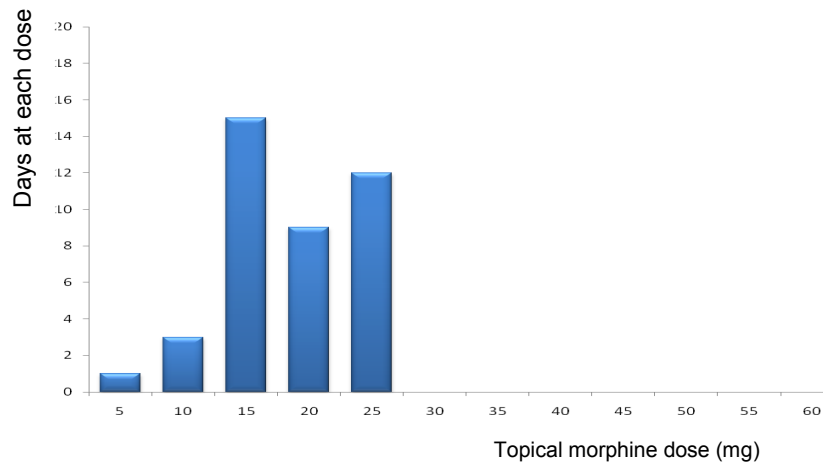
Figure 9.5 Review of clinical protocol for the titration of topically applied opioids: Pre and post titration pain mean NRS (\pm SD) for background and transient pains. (* $p < 0.05$)



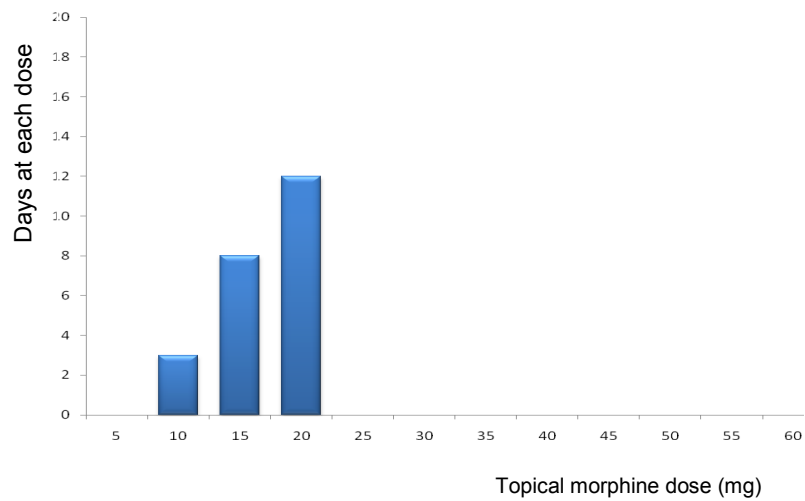
Three patients (11%) had a more protracted titration period [Figure 9.6] which when compared to the other patients did not appear to be related to ulcer aetiology, pain severity, background analgesia or ulcer surface area. Patient 11 was initially titrated to morphine 15 mg and remained at this dose for over two weeks before further increases were required to morphine 20 mg for eight days and then finally 25 mg for 12 days. Patients 19 showed a similar pattern at first morphine 15 mg and then morphine 20 mg. Patient 33 also appeared to require increases after a few days at each dose, before finding the equivalent of morphine 60 mg effective for eight days after which time he was discharged home. These patients may have exhibited tolerance to the topically applied opioid dose although the changes may have been as a result of increased ulcer pain and requiring additional analgesia.

Figure 9.6 Review of clinical protocol for the titration of topically applied opioids: Morphine doses for patients requiring the longest titration periods

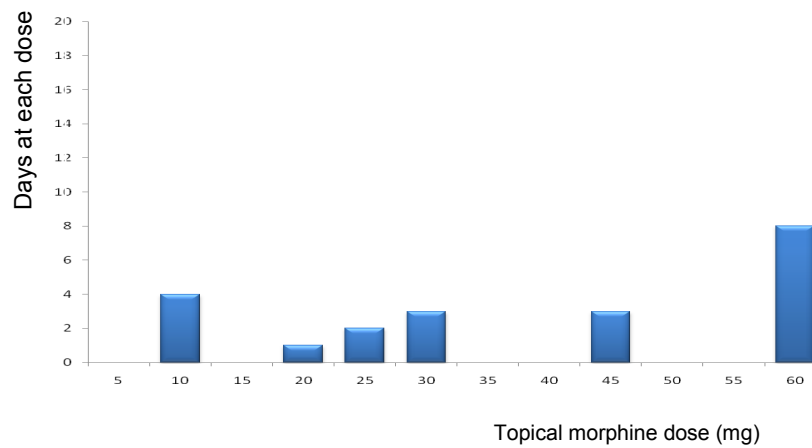
Patient 11



Patient 19



Paient 33



Topically applied opioids appeared to be well tolerated in this patient group. Pruritus was reported in five (19%) patients and burning in three (11%). No systemic adverse effects were documented although most patients were on regular opioid analgesia [Table 9.1] that would have made specific contribution of topical opioids to any systemic adverse effect difficult to determine.

9.5 Discussion

Successful management of pain requires a comprehensive assessment, good communication, education and reassurance of the patient and family, and efforts to encourage the participation of patients and caregivers in the treatment plan. Integral to this plan is the appropriate use of medication that should be administered at the right time at the right dose and for the right patient. In the case of painful chronic wounds where the pathophysiological processes are variable between one patient and another and within the same patient over time, titration of analgesia against an ongoing assessment offers a relatively safe, highly individualised and systematic approach of achieving appropriate management.

Most patients in this review were able to find a successful dose of opioid that was efficacious and well tolerated. Furthermore the dose was reached within a relatively short time. Although some patients appeared to have more variable requirements through a process of re-assessment and ongoing titration they too were able to determine a dose that suited them.

One of the features of wound pain is its variability and three types have been described: cyclic (periodic discomfort), non cyclic (single incident) and chronic (persistent discomfort) (Krasner 1995). The opioid-IntraSite mixture appeared to be effective for both persistent (or

background) and periodic (or transient) discomfort with patients reporting significant falls in pain scores for both pain types. The duration of analgesia provided by the topical administration of opioids appeared to last the 24 hours between dressing changes, which has been reported elsewhere (Krajnik et al. 1999). It is possible that some patients may have managed with less frequent dressing changes. A possible way of testing this would be to apply the two treatments and measure the “time to exit” for each, a method applied elsewhere (Galer et al. 1999) If analgesia does last for several days, this would increase the attractiveness of this treatment option, as provided the reduced frequency was appropriate for the nature of the wound, it would be more convenient for the patient and help reduce nurse workload.

There did not appear to be a simple relationship between the effective dose of topically applied opioids and the patients around the clock medication. A similar finding has been found in other pain states including cancer breakthrough pain (Zeppetella & Ribeiro 2006; Zeppetella 2011). The ability to predict the appropriate dose would make this a more convenient treatment method as patients could be started on pre-determined effective dose. Despite this, most patients were controlled with 10 mg morphine applied daily which suggests that this is a reasonable starting dose that can, following reassessment, be decreased to 5 mg if adverse effects are experienced, or increased in a step-wise fashion as required until successful analgesia is achieved.

In the UK morphine is available as a solution. In most patients 10 mg morphine doses contained within a 1 mL ampoule were used. If higher doses are required the increase in volume can make the mixture more difficult to retain within the wound and contained by the dressing, although morphine is also available in 1 mL ampoules at concentrations of 15, 20 and 30 mg/mL allowing for some flexibility of dosing. Diamorphine, which is available as

an anhydrous powder, is much more soluble than morphine and was therefore used for patient 33 who required higher doses of opioid. Diamorphine degrades first to 6-MAM, and then to morphine and although an equivalence ratio of 1.5 was assumed (Scottish Intercollegiate Guidelines Network 2008), there are not data to support this. Moreover the potency ratios of oral opioids can be variable and depend on both patient and pain related factors (Mercadante & Portenoy 2001). Hence for patient 33 a morphine equivalent dose of 60mg is assumed but it may have been either lower or higher. The benefit of a titration process informed by re-assessment allows for a flexibility of dosing that is responsive to the patient's needs.

The combination of morphine and IntraSite gel is an unlicensed use of a controlled drug. There has been recent concern regarding whether nurses are authorised to prescribe unlicensed medicines, which could be a barrier to the use of morphine mixed and IntraSite gel for painful ulcers. Following clarification by the Medicines and Healthcare products Regulatory Agency (MHRA), it was confirmed that mixing two licensed medicines, where one is not a vehicle for administration of the other, falls within the definition of manufacture and results in a new, unlicensed product being administered (Medicines and Healthcare products Regulatory Agency 2008). The person undertaking this preparation, unless an exemption applies, must hold a manufacturer's licence, although the MHRA recognise that palliative care requires special consideration (Medicines and Healthcare products Regulatory Agency 2009). In the case of morphine and IntraSite gel, the gel is a vehicle for administration and the mixture, therefore, is not considered a new, unlicensed product and can be prepared by nursing staff when required without seeking a manufacturer's licence.

Storage of the mixture will be required in accordance with the statutory regulations.

Schedule 2 drugs such as morphine should be kept in a locked cabinet that should conform

to British Standards and be attached to the fabric of the building. The specifications with which safes, cabinets and rooms must comply are given in detail in the Misuse of Drugs Regulations 2001.

Limitations of this survey are similar to the case review described in Chapter 4 and although the review has the advantage of being practical, feasible to plan, inexpensive, and uses existing records, it relies on the accuracy of written records or recall of individuals and bias is difficult to control as there was no blinding or randomisation, which has been done in the titration process of other pain states (Portenoy et al. 1999). Furthermore although three patients had a lengthy titration process it is not possible to draw conclusion on opioid tolerance, immune suppression or effect (either positive or negative) on healing and how the ulcer had changed over time. Patients were selected for this treatment method if the wound was appropriately managed with IntraSite gel and although a positive effect was found, it is not possible to extrapolate these findings to necrotic or infected ulcers where the use of IntraSite is not indicated.

9.6 Summary

Most hospice in-patients with painful cutaneous ulcers were successfully and safely titrated to a successful dose of topically applied morphine-IntraSite mixture using a clinical titration protocol. Morphine-IntraSite mixture appeared to be effective in most patients, the effective dose low (usually 5-10 mg), unrelated to the background opioid dose and was usually determined within two days of starting titration.

Chapter 10: Discussion

Painful cutaneous ulcers are a heterogeneous group of wounds that represent a significant burden to patients, a clinical challenge for health care professionals and a threat to the health-care economy and resources. Venous ulcers, for example, may be as a result of longstanding venous hypertension leading to hypoxia in areas of venous congestion in the lower extremities, diabetic ulcers occur as a result of neuropathic impairment of musculoskeletal balance as well as immune compromise from leukocyte dysfunction and peripheral vascular disease, pressure ulcers from pressure induced tissue necrosis over a bony prominences, and malignant ulcers arise from primary or secondary cancerous growths. Common to all of these processes is a prolonged inflammatory state comprising a continuous physiological process involving a number of chemical mediators. One of the processes is the migration of opioid receptors to the peripheral nerve endings and has provided the rationale for the direct application of opioid to the wound in the same way the body releases endogenous opioid via the immune system.

There are a number of advantages to the application of topical opioids. For example, they are inexpensive, appear safe, provide localised analgesia, may be systemic, oral or parenteral opioid sparing, give the patient control, and there is little, if any, potential for abuse and addiction (Tennant 2010). Questions however remain to be answered including:

- What are the most efficacious opioid and at what dosages?
- What are the most advantageous carrier and method of application?
- Which pain types are most amenable to topical opioid therapy?
- What degree and duration of analgesic effects might be expected?
- In which circumstances could topical opioids completely replace the need for systemic opioids or other analgesics?

- What is the potential, if any, for developing tolerance or hyperalgesia during prolonged use of topical opioids?

A Cochrane review is currently being planned to provide an overview of the analgesic efficacy and associated adverse events of topical analgesics (including opioids) for the treatment of acute and chronic pain in adults (Moore et al. 2010) and may be helpful in answering some of these questions.

The results of the studies reported in this thesis are limited to the methods employed in each study. For example the efficacy studies cannot be applied to necrotic and infected ulcers, as these ulcers were excluded from the study, nor the use of carriers other than IntraSite gel. Furthermore the physical and microbiological stability studies do not offer information on of the same opioid prepared using different methods or for longer periods of time. Nonetheless the results do provide some support in the palliative care setting for the utility of topically applied morphine for painful pressure ulcers that are neither necrotic nor infected and suitable for treatment with IntraSite gel, and therefore does not support the null hypothesis set out at the beginning of this thesis (see Chapter 3). The results also support the possibility of the opioids having a local action and the practical application of preparing morphine IntraSite gel mixtures in advance rather than just prior to the dressing.

Some aspects of the thesis were more challenging than others. The biochemical bioavailability and stability studies and the microbiological stability studies were relatively straight forward. Generally recognised methods were employed based on previous work and the results, I feel, stand up well to other work in the literature within the limitations of the methods employed, e.g. dose drug. Other aspects of the thesis that were limited by the challenges of undertaking clinical trials in a frail population with multiple co-morbidities, in

particular the efficacy study, which was terminated early because I moved from St Joseph's, where the study was carried out, to St Clare Hospice. The ITT efficacy data suggest that there was a carryover effect of morphine through to the washout period whereas the PP population did not. Furthermore although separate analysis of the pre-washout morphine and placebo arms compared to baseline was strongly significant in favour of morphine this should be taken with caution as the lower number of observations reduced the power of the study. A higher number of patients and a longer washout period may have helped clarify some of the findings. I have attempted to repeat the randomised double blind study in a larger population collaborating with other palliative care units in both the UK and abroad, and working with the Herts and Essex Comprehensive Local Research Network (CLRN), but have been unable to do so. The most promising option was the dermatology speciality at the CLRN and given the opportunity I would wish to explore this further in the future.

The effective dose of morphine in IntraSite gel requires further investigation and although most patients appeared to respond to low doses, this was determined using a retrospective chart review method that has certain limitations. Ideally a prospective randomised double blind study would give more information. All patients could be randomly assigned to begin treatment with either 5 or 10mg morphine in IntraSite gel daily both preparations being identical in appearance and both the patient and the investigator blind to this starting dose. The dose of morphine would then be increased or decreased on successive days in 5mg steps; the 5mg starting dose could be reduced to 2.5mg. The decision to titrate or maintain the dose for another day was made following the assessment that evaluated response to the morphine/IntraSite mixture with the patient. Some titration trials have built in a separate randomisation to include an 'ignore request', i.e. a certain number of requests to increase the dose are ignored and unbeknown to patient and investigator the dose remains unchanged (Portenoy et al. 1999). This second randomisation and blinding procedure,

together with the double-blind random assignment to a starting dose, reduces the likelihood that the patient or investigator would know either the dose or whether it represented a true increase. The titration process continues until the patient finds a successful dose or is deemed to be a non-responder. I feel such a trial would help clarify the issue of the most effective dose.

It is assumed that opioids exert their effect by activating peripheral opioid receptors to produce analgesia by inhibiting the excitability of sensory nerves, the release of excitatory neuropeptides, or both. Because these effects occur in the periphery, they are devoid of central opioid side effects, such as respiratory depression, sedation, or dysphoria (Machelska & Stein 2002). Opioids produce analgesia by increase potassium and decrease calcium currents through interactions with G-proteins in the CNS (Law et al. 2000) and inhibiting calcium currents in the dorsal root ganglion (Atkins & McCleskey 1993). However other mechanisms of action could be implicated in peripheral analgesia and contribute to the results seen in the efficacy studies and our on-going clinical practice.

Methadone, for example, has been shown to have weak NMDA receptor antagonistic activity (Chizh et al 2000; Callaghan et al. 2004)) that may account for some of its effectiveness in neuropathic pain states and contribute to the improvement seen in opioid induced hyperalgesia resulting from opioid switching. Peripherally the NMDA system may interact with other systems including adenosine, which is released locally at sites of cellular trauma, and acts on specific cell-surface purinergic receptors (termed P1 receptors) near its site of release to exert its effects (Kowaluk 1998).

Morphine and other opioids have been shown to modulate immune responses by central and peripheral mechanisms; opioids share many properties of cytokines, the principal

mediators of the immune function. While exogenous opioids mediate immunosuppression, endogenous opiates exert opposite actions; acute and chronic opioid administration is known to have inhibitory effects on humoral and cellular immune responses including antibody production, natural killer cell activity, cytokine expression, and phagocytic activity (Vallejo et al. 2004). One of the possible mechanisms is through hypothalamic-pituitary-adrenal axis leading to increased glucocorticoid production (Zhang et al. 2011) that in turn could have an analgesic effect.

Finally opioids have been shown to induce oxidative stress resulting in generation of free radicals and lipid peroxidation (Zhou et al. 2000), which may be an important where expression of growth factors and new vessel growth can be initiated via inflammatory reactions or oxidative metabolites. Morphine has been shown in vitro to have antioxidant activity (Gülçin et al. 2004), which could interfere with the oxidation process during inflammation by reacting with free radicals, chelating, catalytic metals, and also by acting as oxygen scavengers.

The pathophysiology of peripheral injury and inflammation is complex and includes the release of numerous chemical mediators including K^+ , H^+ , bradykinin, substance P, prostanoids, and cytokines, in addition to the expression of opioids receptors peripherally. It is unlikely that these systems work in isolation and our understanding of the inflammatory processes are limited by the lack of data rather than the potential of the human body. With respect to the opioids receptor contribution to the inflammatory processes, it may be possible to explore this further by determining whether topical analgesia can be reversed by the application of naloxone as has been demonstrated with intra-articular opioids

Treatment options often fall in and out of favour, and over the last 25 years I have been involved in some that have done just that. For example, since I published the initial case series reports of nasal and buccal fentanyl for the management of breakthrough pain (Zeppetella 2000; Zeppetella 2001), the use of transmucosal fentanyl has turned into a major therapeutic area where a number of products exist. On the other hand, the use of nebulised morphine for the management of breathlessness (Zeppetella 1997) has failed to show a consistent benefit and is a treatment I no longer use. My view on the topical application of morphine has evolved over the last ten years. Clearly painful ulcers are difficult to treat, the cause of the pain is multifactorial and dynamic and the treatment should be multimodal. Non-pharmacological treatments (e.g. special mattresses) should be tried, reversible causes (e.g. infection) addressed and adequate analgesia should be prescribed. But in some patients who have tried and not benefitted from these measures and continue to experience inadequate analgesia or have troublesome adverse effects and the wound is suitable for IntraSite dressing, topical application of morphine, as described in this thesis, can be offered.

At the start of this process I was unsure about the utility of topical opioids for painful cutaneous ulcers in our hospice patients, but now, under the right clinical circumstances and whilst we await the publication of further evidence, I would have no hesitation in offering this treatment option to them.

Chapter 11: Conclusions

1. Cutaneous ulcers were found to be common in a patients admitted to a hospice. Most were as a result of pressure and the majority were painful. Patients were seldom prescribed analgesia specifically for the pain resulting from cutaneous ulcers.
2. The evidence from a systematic review of the literature was that the efficacy of topical opioids was largely based on case reports; controlled studies are few and results limited by small patient numbers. In published reports the opioids applied topically appeared to be well tolerated with little or no local or systemic adverse effects reported.
3. Small randomised controlled studies of hospice in-patients with painful cutaneous ulcers suggested that morphine applied topically was an effective method of producing local analgesia, was well tolerated by patients, and was not associated with systemic adverse effects. A review of a titration treatment protocol that had previously been introduced into clinical practice suggested that most patients with painful cutaneous ulcers responded to low doses of topically applied morphine and that there was no simple relationship between the effective dose of topically administered morphine and the dose of regularly scheduled systemic analgesia.
4. When applied topically to cutaneous ulcers, morphine was not absorbed in the majority of patients, suggesting any analgesic effect was mediated locally rather than systemically. However, in ulcers with a large surface area, systemic absorption may occur, however unlikely to result in excessive systemic adverse effects given the relatively small daily dose of morphine applied topically and the fact that most patients with advanced disease are also likely to be on oral opioids.

5. Stability studies indicate that morphine/IntraSite and hydromorphone/IntraSite gel mixtures are stable for up to 28 days irrespective of the temperature and whether or not samples were exposed to light. Diamorphine/IntraSite gel mixture breaks down to 6-MAM, then morphine and no other degradation products are measurable. Oxycodone/IntraSite gel mixture show variability in all gels until day eight after which time concentration of the samples was more stable; no known degradation products are measurable. Morphine/IntraSite mixture was shown to be microbiological stable for up to 28 days if stored in the fridge or at room temperature in the dark.
6. It is not possible to draw conclusions about the type, grade, and area of malignant or non-malignant ulcer that responds best to topical opioid application. Therefore larger prospective, randomised studies are recommended to determine which ulcers respond best to the treatments. Furthermore the effects of topically applied opioids on immune suppression, tolerance and wound healing require further exploration.

Chapter 12: Summary of recommendations for the management of painful cutaneous ulcers with topically applied morphine

12.1 Introduction

The WHO ladder provides a simple framework for the pharmacological management of cancer pain using a logical stepwise approach. The aim is prevent background pain and relieve breakthrough pain by selecting the appropriate analgesic drug, dose and administration route. It is an individualised approach where the patient is titrated to the optimum dose that delivers maximum benefit and tolerable adverse effects. When adverse effects become problematic a switch of administration route may be considered; one potential clinical challenge when this occurs is in the management of painful cutaneous ulcers.

Topical opioids may be considered for the management of painful cutaneous ulcers (e.g. open pressure sores, malignant ulcers, and fungating tumours) in palliative patients where opioids by other routes have proved ineffective or limited by adverse effects. The work presented provides evidence predominantly for this approach in the management of painful pressure ulcers. A systematic approach is recommended where through a sequence of sets the patient's management is individualised [Figure 11.1].

12.2 Assessment

The mainstay of pain assessment is the patient self-report; however, family caregivers are often used as proxies for patient reports, especially in situations in which communication barriers exist, such as cognitive impairment or language difficulties. A variety of tools have been designed to assess pain in cancer e.g. the Brief Pain Inventory (Cleeland 1984), the goal

of which is to characterize the pain and determine its impact on the patient. Assessment follows the usual clinical model of history, examination and relevant investigations and should consider the physical effects/manifestations of pain, the functional effects (interference with activities of daily living), the psychosocial factors (level of anxiety, mood, cultural influences, fears, effects on interpersonal relationships, factors affecting pain tolerance and the spiritual aspects.

12.3 Assess for and minimise risk factors

A number of factors may impair the healing response resulting in chronic wounds including local infection, hypoxia, trauma, foreign bodies, or systemic problems such as diabetes mellitus, malnutrition, immunodeficiency, or medications. In some cases it may be possible to address these specifically, in others, such as malignant wounds, the goal is palliation.

12.4 Indications of topical morphine

Painful cutaneous ulcers in palliative care patients where opioids or other analgesics by alternative routes have proved ineffective or have been limited by adverse effects.

12.5 Preparation of topical morphine/IntraSite mixture

Sterile technique is recommended and two methods are suggested

1. Using a sterile needle and syringe withdraw 10 mg morphine from an ampoule and inject into an 8 g IntraSite gel capsule. Shake well for three minutes. Label capsule morphine/IntraSite gel mixture 0.125%. Use as soon as practical and discard any remaining mixture immediately after use. Alternatively store in a dry cool place in accordance with the organisation's Medicine Management policies and procedure for controlled drugs.

2. Squeeze the contents of an IntraSite gel capsule into a clean container and add 10 mg morphine (10 mg/mL). Mix thoroughly for three minutes. Label container morphine/IntraSite gel mixture 0.125% and use as soon as practical as no microbiological stability data exist. Discard any remaining mixture immediately after use.

12.6 Storage

If prepared on ward or in the patient's home use as soon as practical. If the mixture is prepared using method 1, it can be stored in the fridge for up to 28 days (Chapter 8). The mixture contains a controlled drug and should be handled in accordance with the relevant policies and procedures.

When considering topical opioid administration use morphine sulphate injection

Initially apply morphine 0.125% gel (10 mg/mL morphine sulphate in 8 g IntraSite gel) to the wound once daily. This can be increased to twice or three times daily depending on response; IntraSite gel should be washed off the wound before reapplying the next dose. At doses greater than 30 mg morphine to avoid an excessively fluid mixture switch to a more concentrated morphine preparation. Topical opioids should not be applied to wounds with excessive exudates or bleeding because the gel will not adhere to the wound surface. It is not recommended in patients under the age of 18 because of the lack of data and in patients with a known hypersensitivity to opioids or IntraSite gel. If in doubt seek advice from pharmacy, pain, palliative care or tissue viability teams.

12.7 Titrate topically administered morphine starting from 10mg in 5mg steps

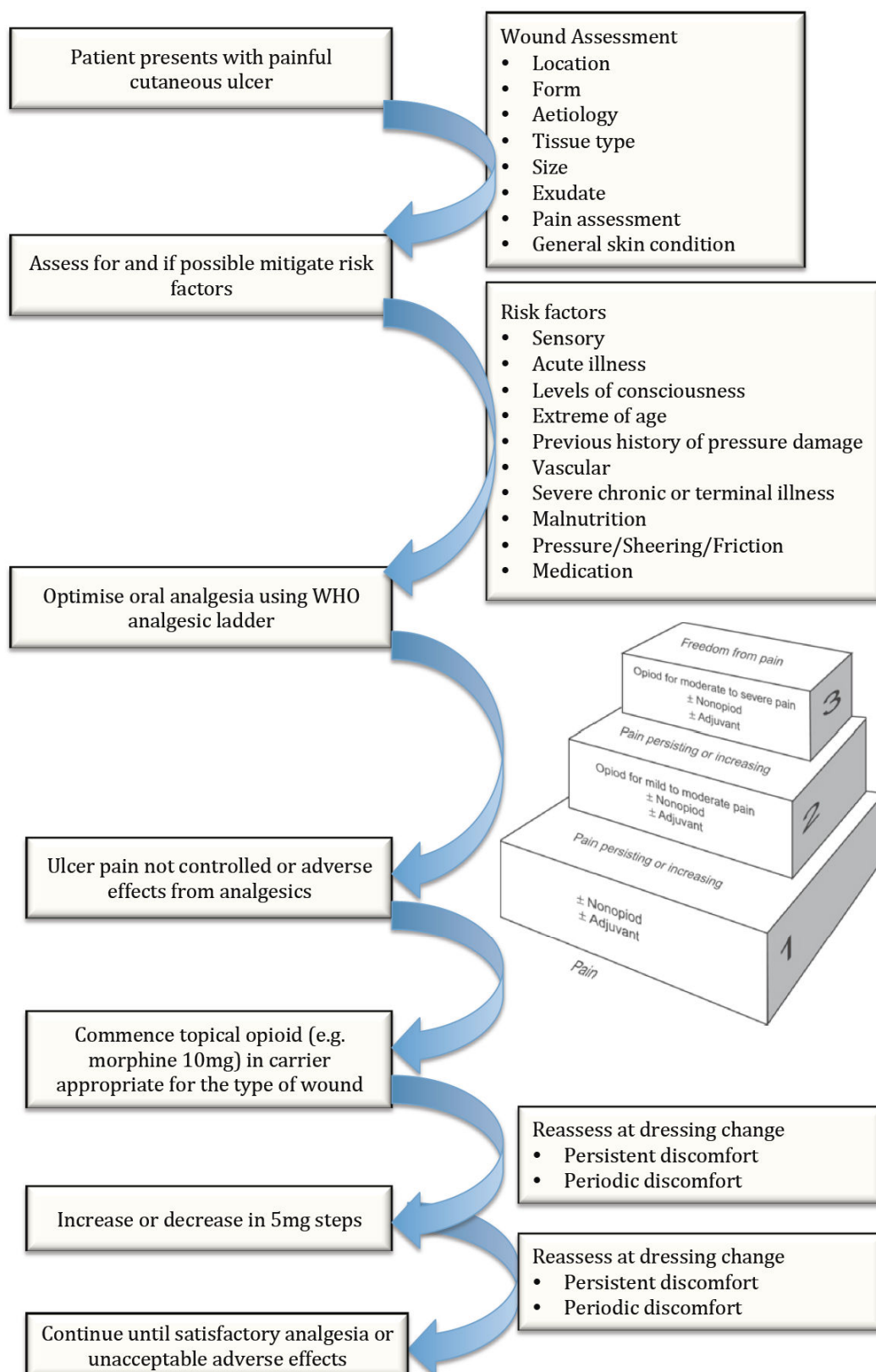
Given the heterogeneity of ulcers a titration process is recommended that is based on a regular reassessment at the dressing change where the opioid dose may be either increased or decreased. Where pain is well controlled for most of the day but pain consistently returns

prior to the dressing change despite an increase in opioids, increasing the frequency of administration to twice or three times daily should be considered.

12.8 Reassessment

Patients should be re-assessed regularly to determine the efficacy and tolerability of the management strategies; inadequate re-assessment may lead to continuance of ineffective and inappropriate treatment. If titration fails to identify a successful dose or if adverse effects become problematic, treatment should be discontinued. Local adverse effects have been reported including pruritus, burning and discomfort. Few systemic adverse effects have been reported in the literature; however the potential exists for systemic absorption, especially treating ulcers with large surface areas.

Figure 11.1 Algorithm for the topical application of morphine for the management of painful cutaneous ulcers



Chapter 13: References

- Abbas SQ. (2004) Diamorphine-Intrasite dressings for painful pressure ulcers. *Journal of Pain and Symptom Management*, 28: 532-534.
- Adderley UJ, Smith R. (2007) Topical agents and dressings for fungating wounds. *Cochrane Database of Systematic Reviews*, Issue 2. Art. No.: CD003948. DOI: 10.1002/14651858.CD003948.pub2.
- Addington-Hall JM, MacDonald LD, Anderson HR et al. (1992) Randomised controlled trial of effects of coordinating care for terminally ill cancer patients. *British Medical Journal*, 305: 1317–1322.
- Akins PT, McCleskey EW. (1993) Characterization of potassium currents in adult rat sensory neurons and modulation by opioids and cyclic AMP. *Neuroscience*, 56: 759-769.
- Alvarez OM, Kalinski C, Nusbaum J et al. (2007) Incorporating wound healing strategies to improve palliation (symptom management) in patients with chronic wounds. *Journal of Palliative Medicine*, 10: 1161-1189.
- Alvarez OM, Meehan M, Ennis W et al. (2002) Chronic wounds: palliative management for the frail population. *Wounds*, 14 (8 Suppl): 4-27.
- Amer S, Meyerson BA. (1988) Lack of analgesic effects of opioids on neuropathic and idiopathic forms of pain. *Pain*, 33: 11-23
- Antonijevic I, Mousa SA, Schäfer M, Stein C. (1995) Perineural defect and peripheral opioid analgesia in inflammation. *The Journal of Neuroscience* 15: 165-172.
- Ashfield T. (2005) The use of topical opioids to relieve pressure ulcer pain. *Nursing Standard*, 9: 90-92.
- Atchison N, Osgood P, Carr B, Szyfelbein S. (1991) Pain during burn dressing change in children: relationship to burn area, depth and analgesic regimens. *Pain*, 47: 41–45.
- Back IN, Finlay I. (1995) Analgesic effect of topical opioids on painful skin ulcers. *Journal of Pain and Symptom Management*, 10: 493.
- Bagnol D, Mansour A, Akil H, Watson SJ. (1997) Cellular localization and distribution of the cloned mu and kappa opioid receptors in rat gastrointestinal tract. *Neuroscience*, 81: 579-591.
- Bahn AN, Michalsen RC. (1961) Addition of bacteriostatic agents to acrylic resins. *The Journal of Prosthetic Dentistry*, 11: 237-243.
- Ballas SK. (2002) Treatment of painful sickle cell leg ulcers with topical opioids. *Blood*, 99: 1096.

- Barker S. (2009) Analgesic effect of locally applied morphine to pyoderma gangrenosum. *Clinical and Experimental Dermatology*, 34, 81–105.
- Barrett DA, Dyssegaard AL, Shaw PN. (1992) The effect of temperature and pH on the deacetylation of diamorphine in aqueous solution and in human plasma. *Journal of Pharmacy and Pharmacology*, 44: 606-608.
- Bastami S, Frödin T, Ahlner J, Uppugunduri S. (2011) Topical morphine gel in the treatment of painful leg ulcers, a double-blind, placebo-controlled clinical trial: a pilot study. *International Wound Journal*, doi: 10.1111/j.1742-481X.2011.00901.x. [Epub ahead of print].
- Bazzicalupo C, Portella A, Contieri M. (1951) Action of propylene glycol upon experimental tuberculosis in guinea pigs. *Proceedings of the Society for Experimental Biology and Medicine*, 78: 671-674.
- Beckett AH, Casey AF. (1954) Synthetic analgesics: stereochemical considerations. *Journal of Pharmacy and Pharmacology*, 6: 986-1001.
- Benbow M. (2009) Assessing the risk of pressure ulcer development. *British Journal of Nursing*, 18: S26-29.
- Bennett G, Moody M. (1995) *Wound care for health care professionals*. London: Chapman Hall.
- Bennett MI. (2006) Diagnosing neuropathic pain in clinical practice. In: Bennet MI (ed.), *Neuropathic Pain*. Oxford Pain Management Library. Oxford University Press, Oxford: 25-35.
- Berezkin VG. (2001) M.S. Tswett's Intellectual Heritage and Modern Chromatography. *Journal of Analytical Chemistry*, 56: 587-592.
- Bidlack JM. (2000). Detection and function of opioid receptors on cells from the immune system. *Clinical and Diagnostic Laboratory Immunology*, 7: 719-723.
- Bigliardi-Qi M, Sumanovski LT, Büchner S, Rufli T, Bigliardi PL. (2004) Mu-opiate receptor and beta-endorphin expression in nerve endings and keratinocytes in human skin. *Dermatology*, 209: 183-189.
- Bijur PE, Latimer CT, Gallagher EJ. (2003) Validation of a verbally administered numerical rating scale of acute pain for use in the emergency department. *Academic Emergency Medicine*, 10: 390-392.
- Binder W, Mousa SA, Sitte N, Kaiser M, Stein C, Schäfer M. (2004) Sympathetic activation triggers endogenous opioid release and analgesia within peripheral inflamed tissue. *European Journal of Neuroscience*, 20: 92-100.

- Bogusz MJ, Maier RD, Schiwy-Bochat KH, Kohls U. (1996) Applicability of various brands of mixed-phase extraction columns for opiate extraction from blood and serum. *Journal of Chromatography B Biomedical Sciences and Applications*, 683: 177-188.
- Breasted JG. (1930) *Ancient Records of Egypt*. University of Chicago Oriental Institute Publications, Vol III. University of Chicago Press.
- Briggs M, Bennett MI, Closs SJ. (2007) Painful leg ulceration: a prospective, longitudinal cohort study. *Wound Repair Regeneration*, 15: 186-191.
- Briggs M, Nelson EA. (2010) Topical agents or dressings for pain in venous leg ulcers. *Cochrane Database of Systematic Reviews Issue 4*. Art. No.: CD001177. DOI: 10.1002/14651858.CD001177.pub2.
- Briggs M, Nelson EA. (2010) Topical agents or dressings for pain in venous leg ulcers. *Cochrane Database Systematic Review*, 4: CD001177.
- British National Formulary. (2011) 61. BMJ Group and the Royal Pharmaceutical Society of Great Britain. 262-272.
- Brogle K, Orna RM, Wu D, Palermo PJ. (1999) Peak fronting in reversed-phase high performance liquid chromatography: a study of the chromatographic behaviour of oxycodone hydrochloride. *Journal of Pharmaceutical and Biomedical Analysis*, 19: 669-678.
- Brose WG, Tanelian DL, Brodsky JB, Mark JB, Cousins MJ. (1991) CSF and blood pharmacokinetics of hydromorphone and morphine following lumbar epidural administration. *Pain*, 45: 11-15.
- Brown G. (2003) Long-term outcomes of full-thickness pressure ulcers: healing and mortality. *Ostomy/Wound Management*, 49: 42-50.
- Brunelli C, Zecca E, Martini C et al. (2010) Comparison of numerical and verbal rating scales to measure pain exacerbations in patients with chronic cancer pain. *Health Quality Life Outcomes*, 8: 42
- Cadet P, Bilfinger TV, Fimiani C, Peter D, Stefano GB. (2000). Human vascular and cardiac endothelia express mu opiate receptor transcripts. *Endothelium*, 7: 185-191.
- Callahan RJ, Au JD, Paul M, Liu C, Yost CS. (2004) Functional inhibition by methadone of N-methyl-D-aspartate receptors expressed in *Xenopus* oocytes: Stereospecific and subunit effects. *Anesthesia and Analgesia*, 98: 653-659.

- Caraceni A, Cherny N, Fainsinger R et al. (2002) Pain measurement tools and methods in clinical research in palliative care: recommendations of an Expert Working Group of the European Association of Palliative Care. *Journal of Pain and Symptom Management*, 23: 239-255.
- Caraceni A, Cherny N, Fainsinger R et al. (2002) Pain measurement tools and methods in clinical research in palliative care: recommendations of an Expert Working Group of the European Association of Palliative Care. *Journal of Pain and Symptom Management*, 23: 239-255.
- Carman CV, Benovic JL. (1998) G-protein-coupled receptors: turn-ons and turn-offs. *Current Opinion in Neurobiology*, 8: 335-344.
- Cassarett DJ, Karlawish JHT. (2000) Are special ethical guidelines needed for palliative care research? *Journal of Pain and Symptom Management*, 20: 130-139.
- Cepeda MS, Africano JM, Polo R, Alcala R, Carr DB. (2003) Agreement between percentage pain reductions calculated from numeric rating scores of pain intensity and those reported by patients with acute or cancer pain. *Pain*, 106: 439-442.
- Cerchietti LC, Navigante AH, Bonomi MR et al. (2002) Effect of topical morphine for mucositis-associated pain following concomitant chemoradiotherapy for head and neck carcinoma. *Cancer*, 95: 2230-2236.
- Cerchietti LC, Navigante AH, Körte MW et al. (2003) Potential utility of the peripheral analgesic properties of morphine in stomatitis-related pain: a pilot study. *Pain*, 105: 265-273.
- Chapman DJ, Cross MJ, Joel SP, Aherne GW. (1995) A specific radioimmunoassay for the determination of morphine-6-glucuronide in human plasma. *Annals of Clinical Biochemistry*, 32: 297-302.
- Chapman DJ, Joel SP, Aherne GW. (1994) Evaluation of a differential radioimmunoassay technique for the determination of morphine and morphine-6-glucuronide in human plasma. *Journal of Pharmaceutical and Biomedical Analysis*, 12: 353-360.
- Charles H. (1995) The impact of leg ulcers on patients' quality of life. *Professional Nurse*, 10: 571-574.
- Chizh BA, Schlütz H, Scheede M, Englberger W. (2000) The N-methyl-D-aspartate antagonistic and opioid components of d-methadone antinociception in the rat spinal cord. *Neuroscience Letters* 22; 296: 117-120.
- Chrisman CA. (2010) Care of chronic wounds in palliative care and end-of-life patients *International Wound Journal*, 7: 214-235.

- Clarkson JE, Worthington HV, Furness S, McCabe M, Khalid T, Meyer S. (2010) Interventions for treating oral mucositis for patients with cancer receiving treatment. Cochrane Database Systematic Review, 4:CD001973.
- Cleeland CS, Ryan KM. (1994) Pain assessment: global use of the Brief Pain Inventory. *Annals of the Academy of Medicine Singapore*, 23: 129-138.
- Coggershall RE, Zhou S, Carlton SM. (1997) Opioid receptors in peripheral sensory axons. *Brain Research*, 764: 126-132.
- Cohen MZ, Easley MK, Ellis C et al. for the JCAHO. (2003) Cancer pain management and the JCAHO's Pain Standards. An institutional challenge. *Journal of Pain Symptom Management*, 25: 519-527.
- Cohen SR, Mount BM, Strobel MG, Bui F. (1995) The McGill Quality of Life Questionnaire: a measure of quality of life appropriate for people with advanced disease. A preliminary study of validity and acceptability. *Palliative Medicine*, 9: 207-219.
- Collier M. (1997) The assessment of patients with malignant fungating wounds - A holistic approach: Part 1. *Nursing Times*, 93 (Suppl): 1-4.
- Collier M. (2003) The elements of wound assessment. *Nursing Times*, 99: 48-49.
- Collin E, Poulain P, Gauvain-Piquard A, Petit G, Pichard-Leandri E. (1993) Is disease progression the major factor in morphine 'tolerance' in cancer pain treatment? *Pain*, 55: 319-326.
- Collins F, Hampton S. White R. (2002) A-Z dictionary of wound care. Quay Books, Mark Allen Publishing Ltd.
- Collins MD, Hoyles L, Foster G, Falsen E. (2004) *Corynebacterium caspium* sp. nov., from a Caspian seal (*Phoca caspica*). *International Journal of Systematic and Evolutionary Microbiology*, 54: 925-928.
- Costantini M, Higginson IJ. (2007) Experimental and quasi-experimental designs. In: Addington-Hall JM, Bruera E, Higginson IJ, Payne S (Eds) *Research methods in palliative care*. Oxford University Press, Oxford: 85-97.
- Cullum N, Deeks JJ, Fletcher AW, Sheldon TA, Song F. (1995) Preventing and treating pressure sores. *Quality in Health Care*, 4: 289-297.
- Czlonkowski A, Stein C, Herz A. (1993) Peripheral mechanisms of opioid antinociception in inflammation: Involvement of cytokines. *European Journal of Pharmacology*, 242: 229-235.

- Davies A, Dickman A, Reid C, Stevens AM, Zeppetella G. (2009) The management of cancer-related breakthrough pain: recommendations of a task group of the Science Committee of the Association for Palliative Medicine of Great Britain and Ireland. *European Journal of Pain*, 13: 331-338.
- Dealey C. (1999) *The care of wounds: A guide for nurses* 2nd edition Blackwell: London
- Deandrea S, Montanari M, Moja L, Apolone G. (2008) Prevalence of undertreatment in cancer pain. A review of published literature. *Annals of Oncology*, 19: 1985-1991.
- DelleMijn P. (1990) Are opioids effective in relieving neuropathic pain? *Pain*, 80: 453-462
- Denyer S, Hodges N. (2004) Sterilization procedures and sterility assurance. In: Denyer SP, Hodges NA, Gorman SP (eds) *Hugo and Russell's Pharmaceutical Microbiology*. 7th edition Blackwell Science Ltd, Oxford: 346-375.
- Department of Health (2010). *The Caldicott Guardian Manual 2010*. Available at: http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/@ps/documents/digitalasset/dh_114506.pdf [accessed 01 July 2012]
- Dickman A. (2010) *Drugs in palliative care*. Oxford University Press: Oxford: 1-15
- Dionne RA, Lepinski AM, Gordon SM, Jaber L, Brahim JS, Hargreaves KM. (2001) Analgesic effects of peripherally administered opioids in clinical models of acute and chronic inflammation. *Clinical Pharmacology and Therapeutics*, 70: 66-73.
- Duncan G, Brooks M. (2009) Chronic wound pain: a literature review. *Wound Practice & Research*, 17: 153-156.
- Durán XN, Ròdenes JL, Isern JC, Torné CM. (2005) Morfina tópica en úlceras dolorosas: a propósito de un caso. *Medicina Palliativa*, 12: 67-69.
- Eisenberg E, McNicol E, Carr DB (2006) Opioids for neuropathic pain. *Cochrane Database Systematic Review*, 3: CD006146.
- Enoch S, Price P (2004) Should alternative endpoints be considered to evaluate outcomes in chronic recalcitrant wounds? *World Wide Wounds*. www.worldwidewounds.com/2004/october/Enoch-Part2/Alternative-Endpoints-To-Healing.html [accessed 01 August 2011].
- European Pharmacopoeia. (2002) Council of Europe, 4th edition, Strasbourg.
- European Wound Management Association. (2002) Position document: pain at wound dressing changes. Medical Education Partnership Ltd, London.
- European Wound Management Association. (2004) Position document: wound bed preparation in practice. Medical Education Partnership Ltd, London.

- Evans E, Gray M. (2005) Do topical analgesics reduce pain associated with wound dressing changes or debridement of chronic wounds? *Journal of Wound Ostomy and Continence Nursing*, 32: 287-290.
- Faller A, Scheunke M. (2004) *The human body*. Thieme, New York: 663-671.
- Farley P. (2011) Should topical opioid analgesics be regarded as effective and safe when applied to chronic cutaneous lesions? *Journal of Pharmacy and Pharmacology*, 63: 747-756.
- Fernández-Natal MI, Sáez-Nieto JA, Fernández-Roblas R et al. (2008) The isolation of *Corynebacterium coyleae* from clinical samples: clinical and microbiological data. *European Journal of Clinical Microbiology and Infectious Diseases*, 27: 177-184.
- Ferris FD, Al Khateib AA, Fromantin I, et al. (2007) Palliative wound care: managing chronic wounds across life's continuum: a consensus statement from international palliative wound care initiative. *Journal of Palliative Medicine*, 10: 37-39.
- Fickel J, Bagnol D, Watson SJ, Akil H. (1997). Opioid receptor expression in the rat gastrointestinal tract: a quantitative study with comparison to the brain. *Brain Research. Molecular brain Research*, 46: 1-8.
- Fields HL, Emson PC, Leigh BK, Gilbert RF, Iversen LL. (1980) Multiple opiate receptor sites on primary afferent nerves. *Nature*, 284: 351-353.
- Flanagan M (2008). Improving wound care teaching and learning in clinical practice. *Wounds UK*, 4: 96-101.
- Flanagan M, Vogensen H, Haase L. (2006) Case series investigating the experience of pain in patients with chronic venous leg ulcers treated with a foam dressing releasing ibuprofen. *World Wide Wounds*
(<http://www.worldwidewounds.com/2006/april/Flanagan/Ibuprofen-Foam-Dressing.html>). [accessed 01 July 2012].
- Flock P, Gibbs L, Sykes N. (2000) Diamorphine-Metronidazole gel effective for treatment of painful infected leg ulcers. *Journal of Pain and Symptom Management*, 20: 396-397.
- Flock P. (2003) Pilot study to determine the effectiveness of diamorphine gel to control pressure ulcer pain. *Journal of Pain and Symptom Management*, 25: 547-554.
- Fowler E, Scott-Williams S, McGuire JB. (2008) Practice Recommendations for Preventing Heel Pressure Ulcers. *Ostomy/Wound Management*, 54: 42-57.
- Franks PJ, Bosanquet N, Connolly M, Oldroyd MI et al. (1995) Venous ulcer healing: effect of socioeconomic factors in London. *Journal of Epidemiology and Community Health*, 49: 385-388.

- Franks PJ, Moffatt CJ, Connolly M et al. (1994) Community leg ulcer clinics: effect on quality of life. *Phlebology*, 9: 83-86.
- Fryirs B, Dawson M, Mather LE. (1997) Highly sensitive gas chromatographic-mass spectrometric method for morphine determination in plasma that is suitable for pharmacokinetic studies. *Journal of Chromatography B, Biomedical Sciences and Applications*, 693: 51-57.
- Funke G, Ramos CP, Collins MD. (1997) *Corynebacterium coyleae* sp. nov., isolated from human clinical specimens. *International Journal of Systematic Bacteriology*, 47: 92-96.
- Furlan AD, Sandoval JA, Mailis-Gagnon A, Tunks E. (2006) Opioids for chronic non cancer pain: a meta-analysis of effectiveness and side effects. *Canadian Medical Association Journal*, 174: 1589-1594.
- Galer BS, Rowbotham MC, Perander J, Friedman E. (1999) Topical lidocaine relieves postherpetic neuralgia more effectively than a vehicle topical patch: results of an enriched enrollment study. *Pain*, 80: 533-538.
- Gallagher RE, Arndt DR, Hunt KL. (2005) Analgesic effects of topical methadone: a case report of four cases. *Clinical Journal of Pain*, 21: 190-192.
- Galvin J. (2002) An audit of pressure ulcer incidence in a palliative care setting. *International Journal of Palliative Nursing*, 8: 214-221.
- Gates M, Tschudi G J. (1952) The synthesis of morphine. *Journal of the American Chemical Society*, 78, 1380-1393.
- Gebauer MG, McClure & Vlahakis TL. (2001) Stability indicating HPLC method for the estimation of oxycodone and lidocaine in rectal gel. *International Journal of Pharmaceutics*, 223: 49-54.
- Gehrke CW, Wixom RL, Bayer E. (Eds) (2001) *Chromatography: A century of discovery (1900-2000)*. *Journal of Chromatography Library* 64. Elsevier Amsterdam.
- George R, Way EL. (1955). Studies on the mechanism of pituitary-adrenal activation by morphine. *British Journal of Pharmacology and Chemotherapy*, 10: 260-264.
- Gilbert PE, Martin WR. (1976) The effects of morphine- and nalorphine-like drugs in the non-dependent morphine-dependent and cyclazocine-dependent chronic spinal dog. *Journal of Pharmacology and Experimental Therapeutics*, 198: 66-82.
- Goldstein A. (1987) Binding selectivity profiles for ligands of multiple receptor types: Focus on opioid receptors. *Trends in Pharmacological Sciences*, 8: 456-459.

- Gorecki C, Brown JM, Nelson EA, et al. (2009) On behalf of the European Quality of Life Pressure Ulcer Project. Impact of pressure ulcers on quality of life in older patients: a systematic review. *Journal of the American Geriatric Society*, 57: 1175-1183.
- Gorecki C, Closs SJ, Nixon J, Briggs M. (2011) Patient-reported pressure ulcer pain: a mixed-methods systematic review. *Journal of Pain Symptom Management*, 42: 443-459
- Gottrup F, Jørgensen B, Karlsmark T et al. (2007) Lower pain with Biatain-Ibu: a randomised, controlled, double-blind clinical investigation on painful venous leg ulcers. *International Wound Journal*, 4 (Suppl. 1): 24–34.
- Gottrup F, Karlsmark T. (2005) Leg ulcers: uncommon presentations. *Clinical Dermatology*, 23: 601–611.
- Grassby PF, Hutchings L. (1993) Factors affecting the physical and chemical stability of morphine sulphate solutions stored in syringes. *International Journal of Pharmacy Practice*, 2: 39-43.
- Grassby PF, Hutchings L. (1997) Drug combinations in syringe drivers: the compatibility and stability of diamorphine with cyclizine and haloperidol. *Palliative Medicine*, 11: 217-224.
- Grey JE, Harding KG, Enoch S. (2006a) Wound assessment. *British Medical Journal*, 332: 285-288.
- Grey JE, Harding KG, Enoch S. (2006b) Pressure ulcers. *British Medical Journal*, 332: 472-475.
- Grocott P. (1997) Evaluation of a tool used to assess the management of fungating wounds. *Journal of Wound Care*, 6: 421-424.
- Grocott P. (2000) Palliative management of fungating malignant wounds. *Journal of Community Nursing*, 14: 31-40.
- Grocott P. (2001) Developing a tool for researching fungating wounds.
<http://www.worldwidewounds.com/2001/july/Grocott/Fungating-Wounds.html>
[accessed 01 July 2012].
- Grocott P. (2007) Care of patients with fungating malignant wounds. *Nursing Standard*, 21: 57-66.
- Grond S, Zech D, Diefenbach C, Radbruch L, Lehmann KA. (1996) Assessment of cancer pain: a prospective evaluation in 2266 cancer patients referred to a pain service. *Pain*, 64: 107-114.
- Gudermann T, Kalkbrenner F, Schultz G. (1996) Diversity and selectivity of receptor-G protein interaction. *Annual Review of Pharmacology and Toxicology*, 36: 429-459.

- Gülçin I, Beydemir S, Alici HA, Elmastaş M, Büyükokuroğlu ME. (2004) In vitro antioxidant properties of morphine. *Pharmacological Research*, 49: 59-66.
- Gulland JM, Robinson R. (1925) Constitution of codeine and thebaine. *Memoirs of the Literary and Philosophical Society of Manchester*, 69: 79-86.
- Guo S, Di Pietro LA. (2010) Factors Affecting Wound Healing. *Journal of Dental Research* 89: 219-229.
- Gupta A, Bodin L, Holmström B, Berggren L. (2001) A systematic review of the peripheral analgesic effects of intraarticular morphine. *Anesthesia and Analgesia*, 93: 761-770.
- Gustafsson LL, Wiesenfeld-Hallin Z. (1988) Spinal opioid analgesia. A critical update. *Drugs*, 35: 597-603.
- Hanks G, De Conno F, Cherny N et al. (2001) Expert Working Group of the Research Network of the European Association for Palliative Care Morphine and alternative opioids in cancer pain the EAPC recommendations. *British Journal of Cancer*, 84: 587-593.
- Hanks GW, Forbes K. (1997) Opioid responsiveness. *Acta Anaesthesiologica Scandinavica*, 41: 154-158.
- Hanks GW. (1991) Opioid-responsive and opioid-non-responsive pain in cancer. *British Medical Bulletin*, 47: 718-731.
- Harrow J. (2011) A comparison of the effects of two hydrogels upon the proliferation of 3 micro-organisms important in chronic wound care <http://wound.smith-nephew.com/au/node.asp?NodeId=3399> [accessed 01 July 2012].
- Hasfield-Wolf ME, Rund C. (1997) Malignancy cutaneous wounds: a management protocol. *Ostomy/Wound Management*, 43: 56-66.
- Hasfield-Wolfe ME, Baxendale-Cox LM. (1999) Staging of malignant cutaneous wounds: a pilot study. *Oncology Nursing Forum*, 26: 1055-1064.
- Hassan AH, Pzewlocki R, Herz A, Stein C. (1992) Dynorphin, a preferential ligand for kappa-opioid receptors is present in nerve fibres and immune cells within inflamed tissue of the rat. *Neurosciences Letters*, 140: 85-88.
- Hatcliffe S, Dawe R. (1996) Monitoring pressure scores in a palliative care setting. *International Journal of Palliative Nursing*, 2: 182-186.
- Heberden W. (1962) Commentaries on the history and cure of disease, Hafner, New York: 213.

- Henoeh I, Gustafsson M. (2003) Pressure ulcers in palliative care: development of a hospice pressure ulcer risk assessment scale. *International Journal of Palliative Nursing*, 9: 474-484.
- Herman A, Botser IB, Tenenbaum S, Chechick A. (2009) Intention-to-treat analysis and accounting for missing data in orthopaedic randomized clinical trials. *Journal of Bone and Joint Surgery*, 91: 2137-2143.
- Hess DR. (2004) Retrospective studies and chart reviews. *Respiratory Care* 49: 1171-1174.
- Heurich M, Mousa SA, Lenzner M et al. (2007) Influence of pain treatment by epidural fentanyl and bupivacaine on homing of opioid-containing leukocytes to surgical wounds. *Brain Behaviour and Immunity*, 21: 544-552.
- Hildebrand KR, Elsberry DE, Anderson VC. (2001) Stability and compatibility of hydromorphone hydrochloride in an implantable infusion system. *Journal of Pain Symptom Management*, 22: 1042-1047.
- Hines S, Pleasance S. (2009) Compatibility of an injectable high strength oxycodone formulation with typical diluents, syringes, tubings, infusion bags and drugs for potential co-administration. *European Journal of Hospital Pharmacy Practice*, 15: 32-38.
- Hjermstad MJ, Fayers PM, Haugen DF et al. (2011) Studies comparing Numerical Rating Scales, Verbal Rating Scales, and Visual Analogue Scales for assessment of pain intensity in adults: a systematic literature review. *Journal of Pain Symptom Management*, 41: 1073-1093.
- Hollis S, Campbell F. (1999) What is meant by intention to treat analysis? Survey of published randomised controlled trials. *BMJ*, 319: 670-674.
- Holzer P. (2004) Opioids and opioid receptors in the enteric nervous system: from a problem in opioid analgesia to a possible new prokinetic therapy in humans. *Neuroscience Letters*, 361: 192-195.
- Hughes J, Smith T, Kosterlitz H, Fothergill L, Morgan B, Morris H. (1975) Identification of two related pentapeptides from the brain with potent opiate agonist activity. *Nature*, 258: 577-580.
- ICH Harmonised Tripartite Guideline. (2003) Stability testing of new substances and products – Q1A (R2) Step 4 version.
- Inturrisi CE, Max MB, Foley KM, Schultz M, Shin SU, Houde RW. (1984) The pharmacokinetics of heroin in patients with chronic pain. *New England Journal of Medicine*, 310: 1213-1217.

- Jacox A, Carr DB, Payne R (1994) New clinical-practice guidelines for the management of pain in patients with cancer. *New England Journal of Medicine*, 330: 651-655.
- Jadad AR, Moore RA, Carroll D et al. (1996) Assessing the quality of reports on randomised clinical trials: Is blinding necessary? *Controlled Clinical Trials*, 17: 1-12.
- Jansen MM, van der Horst JC, van der Valk PG, Kuks PF, Zylicz Z, van Sorge AA. (2009) Pain-relieving properties of topically applied morphine on arterial leg ulcers: a pilot study. *Journal of Wound Care*, 18: 306-312.
- Joel S, Osborne RJ, Slevin M. (1988) An improved method for the simultaneous determination of morphine and its glucuronides metabolites. *Journal of Chromatography*, 430: 394-399.
- Jones V, Milton T. (2000) When and how to use hydrogels. *Nursing Times*, 96: 3-4.
- Jørgensen B, Friis GJ, Gottrup F. (2006) Pain and quality of life for patients with venous leg ulcers: proof of concept of the efficacy of Biatain-Ibu, a new pain reducing wound dressing. *Wound Repair Regeneration*, 14: 233-239.
- Kaasa S, Hjermstad MJ, Loge JH. (2006) Methodological and structural challenges in palliative care: how have we fared in the last decades? *Palliative Medicine*, 20: 727-734.
- Kalso E, Smith L, McQuay HJ, Moore RA. (2002) No pain, no gain: clinical excellence and scientific rigour - lessons learned from IA morphine. *Pain*, 98: 269-275.
- Kapil RP, Padovani PK, King SY, Lam GN, (1992). Nanogram level quantitation of oxycodone in human plasma by capillary gas chromatography using nitrogen-phosphorus selective detection. *Journal of Chromatography*, 577: 283-287.
- Khondkar DK, Chopra P, McArter JP, Rosen JA, Li SK. (2010) Chemical Stability of Hydromorphone Hydrochloride in Patient-Controlled Analgesia Injector. *International Journal of Pharmaceutical Compounding*, 14: 160-164.
- Kinzbrunner BM. (1995) Ethical dilemmas in hospice and palliative care. *Supportive Care in Cancer*, 3: 28-36.
- Klepstad P, Kaasa S, Cherny N, Hanks G, de Conno F, Research Steering Committee of the EAPC. (2005) Pain and pain treatments in European palliative care units. A cross sectional survey from the European Association for Palliative Care Research Network. *Palliative Medicine*, 19: 477-484.
- Knox JH. (1978) High-performance liquid chromatography. Edinburgh University Press
- Kolesnikov Y, Pasternak GW. (1999) Topical opioids in mice: analgesia and reversal of tolerance by topical N-Methyl-D-Aspartate antagonist. *Journal of Pharmacology and Experimental Therapeutics*, 290: 247-252.

- Koneru A, Satyanarayana S, Rizwan S. (2009) Endogenous opioids: Their physiological role and receptors. *Global Journal of Pharmacology*, 3: 149-153.
- Kottner J, Dassen T, Tannen A. (2009) Inter- and intrarater reliability of the Waterlow pressure sore risk scale: a systematic review. *International Journal of Nursing Studies*, 46: 369-379.
- Kowaluk EA. (1998) Adenosine modulation: a novel approach to analgesia and inflammation. *Expert Opinion on Investigational Drugs*, 7: 535-543.
- Krajnik M, Zylicz Z, Finlay I, Luczak J, van Sorge AA. (1999) Potential uses of topical opioids in palliative care - report of 6 cases. *Pain*, 80: 121-125.
- Krajnik M, Zylicz Z. (1997) Topical morphine for malignant cutaneous pain. *Palliative Medicine*, 11: 325.
- Krasner D. (1995) The chronic wound pain experience: a conceptual model. *Ostomy Wound Management*, 41: 20-25.
- Lane P. (2008) Handling drop-out in longitudinal clinical trials: a comparison of the LOCF and MMRM approaches. *Pharmaceutical Statistics*, 7: 93-106.
- Langemo DK. (2006) When the goal is palliative care: *Advances in Skin and Wound Care*, 19: 148-154.
- Law P-Y, Wong YH, Loh HH. (2000) Molecular mechanisms and regulation of opioid receptor signaling. *Annual Review of Pharmacology and Toxicology*, 40: 389-430.
- Le Roux AA. (1993) TELER: The Concept. *Physiotherapy*, 79: 755-758.
- Lee JW, Pedersen JE, Moravetz TL, Dzerk AM, Mundt AD, Shepard KV. (1991) Sensitive and specific radioimmunoassays for opiates using commercially available materials. I: Methods for the determinations of morphine and hydromorphone. *Journal of Pharmaceutical Sciences*, 80: 284-248.
- Leung MK. (1994) Biochemical isolation and detection of morphine. *Advances in Neuroimmunology*, 4: 93-103.
- Loh HH, Ho IK, Cho TM, Lipscomb W. (1973) Estimation of morphine by polyamide mini thin-layer chromatography. *Journal of Chromatography*, 76: 505-508.
- Long TD, Cathers TA, Twillman RK et al. (2001) Morphine-infused silver sulfadiazine (MISS) cream for burn analgesia: a pilot study. *Journal of Burn Care and Rehabilitation*, 22: 118-123.
- Lookingbill DP, Spangler N, Helm KF. (1993) Cutaneous metastases in patients with metastatic carcinoma: a retrospective study of 4020 patients. *Journal of the American Academy of Dermatology*, 29: 228-236.

- Lötsch J, Kobal G, Stockmann A, Brune K, Geisslinger G. (1997) Lack of analgesic activity of morphine-6-glucuronide after short term intravenous administration in healthy volunteers. *Anesthesiology*, 87: 1348-1358.
- Lund-Nielsen B, Müller K, Adamsen L. (2005) Malignant wounds in women with breast cancer: feminine and sexual perspectives. *Journal of Clinical Nursing*, 14: 56-64.
- Machelska H, Mousa SA, Brack A, Schopohl JK, Rittner HL, Schäfer M, Stein C (2002) Opioid control of inflammatory pain regulated by intercellular adhesion molecule-1. *Journal of Neuroscience* 22:5588–5596.
- Machelska H, Stein C. (2002) Immune mechanisms in pain control. *Anesthesia and Analgesia*, 95: 1002-1008
- Maida V, Corbo M, Dolzhykov M, Ennis M, Irani S, Trozzolo L. (2008) Wounds in advanced illness: a prevalence and incidence study based on a prospective case series. *International Wound Journal*, 5: 305-314.
- Maida V, Ennis M, Kuziemy C, Corban J. (2009a) Wounds and survival in cancer patients. *European Journal of Cancer*, 45: 3237-3244.
- Maida V, Ennis M, Kuziemy C, Trozzolo L. (2009b) Symptoms associated with malignant wounds: a prospective case series. *Journal of Pain Symptom Management*, 37: 206-211.
- Maida V. (2009) The Toronto Symptom Assessment System for Wounds: A New Clinical and Research Tool. *Advances in Skin & Wound Care*, 22: 468-474.
- Majuno G. (1975) *The healing hand: man and wound in the ancient world*. Cambridge: Harvard University Press.
- Martin WR, Eades CG, Thompson JA, Huppler RE, Gilbert PE. (1976) The effects of morphine- and nalorphine-like drugs in the non-dependent and morphine dependent chronic spinal dog. *Journal of Pharmacology and Experimental Therapeutics*, 197: 517-532.
- McCorkle R, Benoliel JQ, Donaldson G, Georgiadou F, Moinpour C, Godell B. (1989) A randomized clinical trial of home nursing care for lung cancer patients. *Cancer*, 64: 1375–1382.
- McDonald A, Lesage P. (2006) Palliative management of pressure ulcers and malignant wounds in patients with advanced illness. *Journal of Palliative Medicine*, 9: 285-295.
- McManus J. (2007) Principles of skin and wound care: the palliative approach. *End of Life Care*, 1: 8-19.

- McQuay HJ, Carroll D, Faura CC, Gavaghan DJ, Hand CW, Moore RA. (1990) Oral morphine in cancer pain: influences on morphine and metabolite concentration. *Clinical Pharmacology and Therapeutics*, 48: 236-244.
- McWhinney IR, Bass MJ, Donner A. (1994) Evaluation of a palliative care service: problems and pitfalls. *British Medical Journal*, 309: 1340-1342.
- Medicines and Healthcare products Regulatory Agency. (2008) Proposal for amendments to medicines legislation allowing mixing of medicines in palliative care. Department of Health, London. <http://www.mhra.gov.uk/home/groups/es-policy/documents/publication/con033524.pdf> [accessed 01 July 2012].
- Medicines and Healthcare products Regulatory Agency. (2009) Report of the CHM working group on 'mixing' of medicines. Department of Health, London. <http://www.mhra.gov.uk/home/groups/es-policy/documents/websiteresources/con057289.pdf> [accessed 01 July 2012].
- Meng QC, Cepeda MS, Kramer T, Zou H, Matoka DJ, Farrar J. (2000) High-performance liquid chromatographic determination of morphine and its 3- and 6-glucuronide metabolites by two-step solid-phase extraction. *Journal of Chromatography B, Biomedical Sciences and Applications*, 742: 115-123.
- Mercadante S, Portenoy RK. (2001) Opioid poorly-responsive cancer pain. Part 1: clinical considerations. *Journal of Pain and Symptom Management*, 21: 144-150.
- Minami M, Satoh M. (1995) Molecular biology of the opioid receptors: structures, functions and distributions. *Neuroscience Research*, 23: 121-145.
- Moher D, Hopewell S, Schulz KF et al. (2010) CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *British Medical Journal*, 340: c869.
- Moody ML. (2010) Topical Medications in the Treatment of Pain. *Pain Medicine News*, 8: 15-21.
- Moore RA, Carroll D, Wiffen PJ, Tramer M, McQuay HJ. (1998) A systematic review of topically-applied non-steroidal anti-inflammatory drugs. *British Medical Journal*, 316: 333-338.
- Moore RA, Derry S, McQuay HJ. Topical Analgesics for Acute and Chronic Pain in Adults (Protocol). *Cochrane Database of Systematic Reviews* 2010, Issue 7, Art No: CD008609DOI: 10.1002/14651858.CD008609.
- Mousa SA, Cheppudira BP, Shaqura M et al. (2007) Nerve growth factor governs the enhanced ability of opioids to suppress inflammatory pain. *Brain*, 130: 502-513.

- Mousa SA, Straub RH, Schafer M, Stein C. (2007) Beta-endorphin, Met-enkephalin and corresponding opioid receptors within synovium of patients with joint trauma, osteoarthritis and rheumatoid arthritis. *Annals of the Rheumatic Diseases*, 66: 871-879.
- Mousa SA, Zhang Q, Sitte N, Ji R, Stein C. (2001) beta-Endorphin-containing memory-cells and mu-opioid receptors undergo transport to peripheral inflamed tissue. *Journal of Neuroimmunology*, 115: 71-78.
- Nassr S, Dubuc MC, Lavoie P & Brazier JL. (2003) HPLC-DAD Methods for studying the stability of solutions containing hydromorphone, ketorolac, haloperidol, midazolam, famotidine, metoclopramide, dimenhydrinate and scopolamine. *Journal of Liquid Chromatography & Related Technologies*, 26: 2909-2929.
- National Pressure Ulcer Advisory Panel. (2007) Pressure definition and stages revised by NPUAP. www.npuap.org/documents/PU_Definition_Stages.pdf. [accessed 01 August 2011].
- Naylor W. (2002) Malignant wounds: Aetiology and principles of management. *Nursing Standard*, 16: 45-56.
- NHS Institution for Innovation and Improvement. (2009) Increasing pressure ulcer reporting within community services. Available at: http://www.institute.nhs.uk/hia_-_your_skin_matters/your_skin_matters/increasing-pressure-ulcer-reporting-within-community-services.html [accessed 01 July 2012].
- Oken MM, Creech RH, Tormey DC et al. (1982) Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. *American Journal of Clinical Oncology*, 5: 649-655.
- Omar OA, Hoskin PJ, Johnston A, Hanks GW, Turner P. (1989) Diamorphine stability in aqueous solution for subcutaneous infusions. *Journal of Pharmacy and Pharmacology*, 41: 275-277.
- Palao i Domenech R, Romanelli M, Tsiftsis DD et al. (2008) Effect of an ibuprofen-releasing foam dressing on wound pain: a real-life RCT. *Journal of Wound Care*, 17: 342, 344-8.
- Pancorbo-Hidalgo PL, Garcia-Fernandez FP, Lopez-Medina IM, Alvarez-Nieto C. (2006) Risk assessment scales for pressure ulcer prevention: a systematic review. *Journal of Advanced Nursing*, 54:94-110.
- Pasternak GW. (1993) Pharmacological mechanisms of opioid analgesics. *Clinical Neuropharmacology*, 16: 1-18.
- Paul J. (2000) Fentanyl topical gel for painful skin ulcers. *Palliative Medicine*, 14: 335.

- Pawula M, Barrett DA, Shaw PN. (1993) An improved extraction method for HPLC determination of morphine and its metabolites in plasma. *Journal of Pharmaceutical and Biomedical Analysis*, 11: 401-406.
- Payne HAS, Tempest SM. (1988) The chemistry and pharmacy of diamorphine. In Scott DB (ed). *Diamorphine*. Cambridge: Woodhead-Faulkner: 1-14.
- Payne WG, Naidu DK, Wheeler CK et al. (2008) Wound healing in patients with cancer. *Eplasty*, 11: 68-90.
- Penson RT, Joel SP, Bakhshi K, Clark SJ, Langford RM, Slevin ML. (2000) Randomized placebo-controlled trial of the activity of the morphine glucuronides. *Clinical Pharmacological Therapeutics*, 68: 667-676.
- Penson RT, Joel SP, Clark S, Gloyne A, Slevin ML. (2001) Limited phase I study of morphine-3-glucuronide. *Pharmaceutical Science*, 90: 1810-1816.
- Penson RT, Joel SP, Roberts M, Gloyne A, Beckwith S, Slevin ML. (2002) The bioavailability and pharmacokinetics of subcutaneous, nebulized and oral morphine-6-glucuronide. *British Journal of Clinical Pharmacology*, 53: 347-354.
- Pert CB, Snyder SH. (1973) Opiate receptor: Its demonstration in nervous tissue. *Science*, 179: 1011-1014.
- Pieper B, Langemo D, Cuddigan J. (2009) Pressure ulcer pain: a systematic literature review and National Pressure Ulcer Advisory Panel white paper. *Ostomy/Wound Management*, 55: 16-31.
- Platzer M, Likar R, Stein C, Beubler E, Sittl R. (2005) Topical application of morphine gel in inflammatory mucosal and cutaneous lesions. *Schmerz*, 19: 296-301.
- Poochikian GK, Cradock JC, Davignon JP. (1983) Heroin: stability and formulation approaches. *International Journal Pharmaceutics*, 13: 219-226.
- Poochikian GK, Cradock JC. (1979) Simple high-performance liquid chromatographic method for the separation of 3,6-diacetylmorphine hydrochloride (heroin) and hydrolysis products. *Journal of Chromatography*, 171: 371-376.
- Poonawala T, Levay-Young BK, Hebbel RP, Gupta K. (2005) Opioids heal ischemic wounds in the rat. *Wound Repair and Regeneration*, 13: 165-174.
- Portenoy RK, Foley KM, Inturrisi CE. (1990) The nature of opioid responsiveness and its implications for neuropathic pain: new hypotheses derived from studies of opioid infusions. *Pain*, 43: 273-286.

- Portenoy RK, Payne R, Coluzzi P et al. (1999) Oral transmucosal fentanyl citrate (OTFC) for the treatment of breakthrough pain in cancer patients: a controlled dose titration study. *Pain*, 79: 303-312.
- Portoghesi PS. (1965) A new concept on the mode of interaction of narcotic analgesics with receptors. *Journal of Medicinal Chemistry* 8: 809-816.
- Porzio G, Aielli F, Verna L, Cannita K, Marchetti P, Ficorella C. (2005) Topical morphine in the treatment of painful ulcers. *Journal of Pain and Symptom Management*, 30: 304-305.
- Poyhia R, Vainio A, Kalso E. (1993). A review of oxycodone's clinical pharmacokinetics and pharmacodynamics. *Journal of Pain Symptom Management*, 8: 63-67.
- Price P, Fogh K, Glynn C, Krasner DL, Osterbrink J, Sibbald RG. (2007) Managing painful chronic wounds: the Wound Pain Management Model. *International Wound Journal*, 4 (Suppl 1): 4-15.
- Price P, Harding K. (2004) Cardiff Wound Impact Schedule: the development of a condition-specific questionnaire to assess health-related quality of life in patients with chronic wounds of the lower limb. *International Wound Journal*, 1: 10-17.
- Price P, Harding KG. (1996) Measuring health-related quality of life in patients with chronic leg ulcers. *Wounds*, 8: 91-94.
- Puehler W, Zöllner C, Brack A, Shaqura MA, Krause H, Schäfer M, Stein C. Rapid upregulation of mu opioid receptor mRNA in dorsal root ganglia in response to peripheral inflammation depends on neuronal conduction. *Neuroscience*. 2004; 129:473-479.
- Racz H, Gunning K, Della Santa D, Forster A. (1991) Evaluation of the effect of perineuronal morphine on the quality of postoperative analgesia after axillary plexus block: a randomized double-blind study. *Anesthesia and Analgesia*, 72: 769-772.
- Reddy M, Kohr R, Queen D, Keast D, Sibbald RG. (2003) Practical treatment of wound pain and trauma: a patient-centered approach. *Ostomy/Wound Management*, 49: 2S-15S.
- Reifsnyder J, Hoplamazian LM, Maxwell TL. (2004) Preventing and treating pressure ulcers in hospice patients. *Caring*, 423: 30-37.
- Reifsnyder J, Magee, H. (2005) Development of pressure ulcers in patients receiving home hospice care. *Wounds*, 17: 74-79.
- Resine T, Pasternak G. (1996) Opioid analgesics and antagonists. In: Gilman AG, Hardman JG, Limbird LE (eds) *Goodman and Gilman's the Pharmacological Basis of Therapeutics*, 9th edition. New York: McGraw Hill: 1026-1038.

- Ribeiro MD, Joel SP, Zeppetella G. (2004) The bioavailability of morphine applied topically to cutaneous ulcers. *Journal of Pain Symptom Management*, 27: 434-439.
- Rinck GC, Van den Bos GAM, Kleijnen J, de Haes HJCM, Schade E, Veenhof CHN. (1997) Methodological issues in effectiveness research on palliative cancer care: A systematic review. *Journal of Clinical Oncology*, 15: 1697–1707.
- Rittner HL, Brack A, Stein C. (2008) Pain and the immune system. *British Journal of Anaesthesia*, 101: 40-44.
- Robson MC, Cooper DM, Aslam R. et al. (2006). Guidelines for the treatment of venous ulcers. *Wound Repair and Regeneration*, 14: 649-662.
- Rogers EA, Das A, Ton-That H. (2011) Adhesion by pathogenic *Corynebacteria*. In; Linke D, Goldman A (eds) *Bacteria adhesion, chemistry, biology and physics*. Springer Science Business + Media BV, Heidelberg: 91-103.
- Romanelli M, Dini V, Polignano R, Bonadeo P, Maggio G. (2009) Ibuprofen slow-release foam dressing reduces wound pain in painful exuding wounds: preliminary findings from an international real-life study *Journal of Dermatological Treatment*, 20: 19-26.
- Romberg R, Olofsen E, Sarton E, den Hartigh J, Taschner PE, Dahan A. (2004) Pharmacokinetic–pharmacodynamic modeling of morphine-6-glucuronide- induced analgesia in healthy volunteers: absence of sex differences. *Anesthesiology*, 100: 120-133.
- Rook JM, Hasan W, McCarson KE. (2008) Temporal effects of topical morphine application on cutaneous wound healing. *Anesthesiology*, 109: 130-136.
- Rook JM, Hasan W, McCarson KE. (2009) Morphine-induced early delays in wound closure: involvement of sensory neuropeptides and modification of neurokinin receptor expression. *Biochemical Pharmacology*, 77: 1747-1755.
- Rook JM, McCarson KE. (2007) Delay of cutaneous wound closure by morphine via local blockade of peripheral tachykinin release. *Biochemical Pharmacology*, 74: 752-757.
- Rossi GC, Brown GP, Leventhal L, Yang K, Pasternak GW. (1996) Novel receptor mechanism for heroin and morphine-6 beta-glucuronide. *Neuroscience Letters*, 216: 1-4.
- Rowbotham MC, Twilling L, Davies PS, Reisner L, Taylor K, Mohr D. (2003) Oral opioid therapy for chronic peripheral and central neuropathic pain. *New England Journal of Medicine*, 348: 1223-1232.
- Sarhill N, Walsh D, Nelson KA. (2001) Hydromorphone: pharmacology and clinical applications in cancer patients. *Supportive Care in Cancer*, 9: 84-96.

- Schiff PL. (2002) Opioids and its alkaloids. American Journal of Pharmaceutical Education, 66: 186-194.
- Schmitt TK, Mousa SA, Brack A et al. (2003) Modulation of peripheral endogenous opioid analgesia by central afferent blockade. Anesthesiology, 98: 195-202.
- Schulz V, Triska OH, Tonkin K. (2002) Malignant wounds: caregiver-determined clinical problems. Journal of Pain Symptom Management, 24: 572-577.
- Scottish Intercollegiate Guidelines Network (2008) Control of pain in adult patients with cancer. A national clinical guidelines <http://www.sign.ac.uk/pdf/SIGN106.pdf> [accessed 01 July 2012].
- Scottish Intercollegiate Guidelines Network. (2008) SIGN 50: A guideline developer's handbook. Scottish Intercollegiate Guidelines Network, Edinburgh <http://www.sign.ac.uk/pdf/sign50.pdf> [accessed 01 July 2012].
- Sehgal N, Smith HS, Manchikanti L. (2011) Peripherally acting opioids and clinical implications for pain control. Pain Physician, 14): 249-258.
- Shafer SL, Varvel JR. (1991) Pharmacokinetics, pharmacodynamics, and rational opioid selection. Anesthesiology, 74: 53-63.
- Simon EJ, Hiller JM, Edelman I. (1973) Stereospecific binding of the potent narcotic analgesic [³H]etorphine to rat-brain homogenate. Proceedings of the National Academy of Sciences of the United States of America, 70: 1947-1949.
- Sitte N, Busch M, Mousa SA et al. (2007) Lymphocytes upregulate signal sequence-encoding proopiomelanocortin mRNA and beta-endorphin during painful inflammation in vivo. Journal of Neuroimmunology, 183: 133-145.
- Skarke C, Darimont J, Schmidt H, Geisslinger G, Lötsch J. (2003) Analgesic effects of morphine and morphine-6-glucuronide in a transcutaneous electrical pain model in healthy volunteers. Clinical Pharmacological Therapeutics, 73: 107-121.
- Skiveren J, Haedersdal M, Philipsen PA et al. (2006) Morphine gel 0.3% does not relieve pain during topical photodynamic therapy: a randomized, double-blind, placebo controlled study. Acta Dermato-Venereologica, 86: 409-411.
- Smeenk FWJM, van Haastregt JCM, de Witte LP, Crebolder HFJM. (1998) Effectiveness of home care programmes for patients with incurable cancer on their quality of life and time spent in hospital: a systematic review. British Medical Journal, 316: 1939-1944.
- Smith MT, Ross FB, Nielsen CK, Saini K. (2001) Oxycodone has a distinctly different pharmacology from morphine. European Journal of Pain, 15 (suppl A): 135-136.

- Soper CJ, Davies DJG (1990) Principles of sterilization. In: Denyer SP, Baird RM (eds) Guide to microbiological control in pharmaceuticals. Ellis Horwood, Chichester: 157-181.
- Stein C, Hassan AH, Lehrberger K, Giefing J, Yassouridis A (1993) Local analgesic effect of endogenous opioid peptides. *Lancet* 342:321–324.
- Stein C, Schäfer M, Hassan AH. (1995) Peripheral opioid receptors. *Annals of Medicine*, 27: 219-221.
- Stein C, Schäfer M, Machelska H. (2003) Attacking pain at its source: new perspectives on opioids. *Nature Medicine*, 9: 1003-1008.
- Stein C. (1995) The control of pain in peripheral tissue by opioids. *New England Journal of Medicine*, 332: 1685-1690.
- Stotter A, Kroll S, McNeese M, Holmes F, Oswald MJ, Romsdahl M. (1991) Salvage treatment for loco-regional recurrence following breast conservation therapy for early breast cancer. *European Journal of Surgical Oncology*, 17: 231–236.
- Streiner DL. (2002) The case of the missing data: methods of dealing with dropouts and other research vagaries. *Canadian Journal of Psychiatry*, 47: 68-75.
- Stuart- Harris R, Joel SP, McDonald P, Currow D, Slevin ML (2000). The pharmacokinetics of morphine and morphine glucuronide metabolites after subcutaneous bolus injection and subcutaneous infusion of morphine. *British Journal of Clinical Pharmacology*, 49: 207-214.
- Sun WM, Read NW, Verlinden M. (1997) Effects of loperamide oxide on gastrointestinal transit time and anorectal function in patients with chronic diarrhoea and faecal incontinence. *Scandinavian Journal of Gastroenterology*, 32: 34-38.
- Tennant F, Moll D, DePaulo V. (1993) Topical morphine for peripheral pain. *The Lancet*, 342: 1047-1048.
- Tennant F. (2010) Taking Advantage of the Peripheral Opioid Receptor. *Practical Pain Management*, 10: 28-30.
- Terenius L. (1973) Stereospecific interaction between narcotic analgesics and a synaptic plasma membrane fraction of rat cerebral cortex. *Acta Pharmacologica et Toxicologica*, 32: 317-320.
- Thomas S, Hay P (1995). Fluid handling properties of hydrogel dressings. *Ostomy/Wound Management*, 41: 54-6 – 58-9.
- Tippet AW. (2005) Wounds at the end of life. *Wounds*, 17: 91-98.
- Touche Ross. (1993) The costs of pressure sores. Report to the Department of Health. Touché Ross & Company: London.

- Tran QNH, Fancher T. (2007) Achieving analgesia for painful ulcers using topically applied morphine gel. *Journal of Supportive Oncology*, 5: 289-293.
- Trengove NJ, Stacey MC, Macauley S et al. (1999) Analysis of the acute and chronic wound environments: the role of proteases and their inhibitors. *Wound Repair and Regeneration*, 7: 442-452.
- Trissel LA Xu QA, Pham L. (2002a) Physical and chemical stability of morphine sulfate 5-mg/mL and 50-mg/mL packaged in plastic syringes. *International Journal of Pharmaceutical Compounding*, 6: 62-65.
- Trissel LA Xu QA, Pham L. (2002b) Physical and chemical stability of low and high concentrations of morphine sulfate with bupivacaine hydrochloride packaged in plastic syringes. *International Journal of Pharmaceutical Compounding*, 6: 70-73.
- Trissel LA Xu QA, Pham L. (2002c) Physical and chemical stability of hydromorphone hydrochloride 1.5- and 80-mg/mL packaged in plastic syringes. *International Journal of Pharmaceutical Compounding*, 6: 74-76.
- Turnbull K, Bielech M, Walker SE, Law S. (2002) Stability of oxycodone hydrochloride for injection in dextrose and saline solutions. *Canadian Journal of Hospital Pharmacy*, 55: 272-277.
- Twillman RK, Long TD, Cathers TA, Mueller DW. (1999) Treatment of painful skin ulcers with topical opioids. *Journal of Pain and Symptom Management*, 17: 288-292.
- Vallejo R, de Leon-Casasola O, Benyamin R. (2004) Opioid therapy and immunosuppression: a review. *American Journal of Therapeutics*, 11: 354-365.
- van Ingen IL, Jansen MM, Barrera P. (2008) Topical opioids for painful ulcers in systemic sclerosis. *Annals of Rheumatic Diseases*, 67: 427.
- Vanderwee K, Clark M, Dealey C, Gunningberg L, Defloor T. (2007a) Pressure ulcer prevalence in Europe: a pilot study. *Journal of Evaluation in Clinical Practice*, 13: 227-235.
- Vanderwee K, Grypdonck M, Defloor T. (2007b) Non-blanchable erythema as an indicator for the need for pressure ulcer prevention: a randomized-controlled trial. *Journal of Clinical Nursing*, 16: 325-335.
- Vascello L, McQuillan RJ. (2006) Opioid analgesics and routes of administration. In: deLeon-Casasola (ed) *Cancer pain. Pharmacological, interventional and palliative care approaches*. Elsevier, Philadelphia: 171-193.

- Vayne-Bossert P, Escher M, de Vautibault CG et al. (2010) Effect of topical morphine (mouthwash) on oral pain due to chemotherapy- and/or radiotherapy-induced mucositis: a randomized double-blinded study. *Journal of Palliative Medicine*, 13: 125-128.
- Vecchio M, Walker SE, Iazzetta J, Hardy BG. (1988) The stability of intravenous infusion solutions. *Canadian Journal of Hospital Pharmacy*, 41: 5-9.
- Velnar T, Bailey T, Smrkolj V. (2009) The wound healing process: an overview of the cellular and molecular mechanisms. *Journal of International Medical Research*, 37: 1528-1542.
- Vermeire A, Remon JP. (1999) Stability and compatibility of morphine. *International Journal of Pharmaceutics*, 187: 17-51.
- Vernassiere C, Cornet C, Trechot P et al. (2005) Study to determine the efficacy of topical morphine on painful chronic skin ulcers. *Journal of Wound Care*, 14: 289-283.
- Vernon T. (2000) IntraSite Gel and IntraSite Conformable: the hydrogel range. *British Journal of Nursing*, 9: 1083-1088.
- Vetter N, Matthew I. (1999) *Epidemiology and Public Health Medicine*. Edinburgh: Churchill Livingstone.
- Von Roenn JH, Cleeland CS, Gonin R, Hatfield AK, Pandya, KJ. (1993) Physician attitudes and practice in cancer pain management: a survey from the Eastern Cooperative Oncology Group. *Annals of Internal Medicine*, 119: 121-126.
- Walker S, DeAngelis and Iazzetta J. (1991) Stability and compatibility of combinations of hydromorphone and a second drug. *The Canadian Journal of Hospital Pharmacy*, 44: 289-295.
- Wang SY, Tham SY, Poon MK. (1986) Thin-layer chromatographic and column liquid chromatographic analyses of morphine in urine via dabsylation. *Journal of Chromatography*, 381: 331-341.
- Ward S, Goldberg N, Miller-McCauley V, et al. (1993) Patient-related barriers to management of cancer pain. *Pain*, 52: 319-324.
- Ware JH. (2003) Interpreting incomplete data in studies of diet and weight loss. *New England Journal of Medicine*, 348: 2136-2137.
- Wasels R, Belleville F, Paysant P, Nabet P, Krakowski I. (1989) Determination of morphine in plasma by gas chromatography using a macrobore column and thermoionic detection after Extrelut column extraction: application to follow-up morphine treatment in cancer patients. *Journal of Chromatography*, 489: 411-418.

- Wasels R, Belleville F. (1994) Gas chromatographic-mass spectrometric procedures used for the identification and determination of morphine, codeine and 6-monoacetylmorphine. *Journal of Chromatography A*, 674: 225-234.
- Watson NW, Taylor KM, Joel SP, Slevin ML, Eden OB. (1996) A pharmacokinetic study of sublingual aerosolized morphine in healthy volunteers. *Journal of Pharmaceutical Pharmacology*, 48: 1256-1259.
- Watterson G, Howard R, Goldman A. (2004) Peripheral opioids in inflammatory pain. *Archives of Disease in Childhood*, 89: 697-681.
- Welling A. (2007) A randomised controlled trial to test the analgesic efficacy of topical morphine on minor superficial and partial thickness burns in accident and emergency departments. *Emergency Medicine Journal*, 24: 408-412.
- Westerling D, Hoglund P, Lundin S, Svedman P. (1994) Transdermal administration of morphine to healthy subjects. *British Journal of Clinical Pharmacology*, 37: 571-576.
- Whitney J, Phillips L, Aslam R et al. (2006) Guidelines for the treatment of pressure ulcers. *Wound Repair and Regeneration*, 14: 663-679.
- Wilkes L, White K, Smeal T, Beale B. (2001) Malignant wound management: What dressings do nurses use? *Journal of Wound Care*, 10: 65-69.
- Wlaschek M, Scharffetter-Kochanek K. (2005) Oxidative stress in chronic venous leg ulcers. *Wound Repair and Regeneration*, 13: 452-461.
- Woo KY, Sibbald RG, Fogh K et al. (2008) Assessment and management of persistent (chronic) and total wound pain. *International Wound Journal*, 5: 205-215.
- Wood A. (1885) New method of treating neuralgia by the direct application of opiates to the painful points, *Edinburgh Medical Surgical Journal*, 82: 265-281.
- World Health Organization. (1986) Cancer pain relief. Geneva: World Health Organization.
- World Health Organization. (1996) Cancer Pain Relief, 2nd edition. Geneva: World Health Organization.
- World Health Organization. (2002) National cancer control programmes: policies and managerial guidelines. Geneva: World Health Organization.
- World Health Organization. (2006) Expert Committee on Specifications for Pharmaceutical Preparations, 40th Report, Technical Report Series No 937. Geneva: World Health Organization.

- Worley CA. (2011) Palliative wound and skin issues. In: Loitman JE, Sinclair CT, Fisch MJ (eds) Palliative care, a case based guide. Springer Science + Business Media, LLC, New York: 63-71.
- Wright AW, Lawrence JA, Lu M, Cramond T, Smith MT. (1998) Solid-phase extraction method with high-performance liquid chromatography and electrochemical detection for the quantitative analysis of oxycodone in human plasma. *Journal of Chromatography B, Biomedical Sciences and Applications*, 712: 169-175.
- Xu QA, Trissel LA, Pham L. (2002) Physical and chemical stability of low and high concentrations of morphine sulfate with clonidine hydrochloride packaged in plastic syringes. *International Journal of Pharmaceutical Compounding*, 6: 66-69.
- Yeh SY, Lach JL. (1961) Stability of morphine in aqueous solution. III. Kinetics of morphine degradation in aqueous solution. *Journal of Pharmaceutical Sciences*, 50: 35-42.
- Zaidi Z, Lanigan SW. (2010) *Dermatology in clinical practice*. Springer-Verlag London Limited: 1-15.
- Zech DF, Grond S, Lynch J, Hertel D, Lehmann KA. (1995) Validation of World Health Organization Guidelines for cancer pain relief: a 10-year prospective study. *Pain*, 63: 65-76.
- Zeppetella G, O'Doherty CA, Collins S. (2000) Prevalence and characteristics of breakthrough pain in cancer patients admitted to a hospice. *Journal of Pain and Symptom Management*, 20: 87-92.
- Zeppetella G, O'Doherty CA, Collins S. (2001) Prevalence and characteristics of breakthrough pain in patients with non-malignant terminal disease admitted to a hospice. *Palliative Medicine*, 15: 243-246.
- Zeppetella G, Porzio G, Aielli F. (2007) Opioids applied topically to painful cutaneous malignant ulcers in a palliative care setting. *Journal of Opioid Management*, 3: 161-166.
- Zeppetella G, Ribeiro MDC. (2006) Opioids for the management of breakthrough (episodic) pain in cancer patients. *The Cochrane Database of Systematic Reviews Issue 1*. Art. No.: CD004311. DOI: 10.1002/14651858.CD004311.pub2.
- Zeppetella G. (1997) Nebulized morphine in the palliation of dyspnoea. *Palliative Medicine*, 11: 267-275.
- Zeppetella G. (2000) An assessment of the safety, efficacy, and acceptability of intranasal fentanyl citrate in the management of cancer-related breakthrough pain: a pilot study. *Journal of Pain and Symptom Management*, 20: 253-258.

- Zeppetella G. (2001) Sublingual fentanyl citrate for cancer-related breakthrough pain: a pilot study. *Palliative Medicine*, 15: 323-328.
- Zeppetella G. (2011) Opioids for the management of breakthrough cancer pain in adults: a systematic review undertaken as part of an EPCRC opioid guidelines project. *Palliative Medicine*, 25: 516-524.
- Zhang EY, Xiong J, Parker BL et al. (2011) Depletion and recovery of lymphoid subsets following morphine administration. *British Journal of Pharmacology*, 164: 1829-1844.
- Zhou JF, Yan XF, Ruan ZR et al. (2000) Heroin abuse and nitric oxide, oxidation, peroxidation, lipoperoxidation. *Biomedical and Environmental Sciences*, 13: 131-139.
- Zhou L, Zhang Q, Stein C, Schäfer M. (1998) Contribution of opioid receptors on primary afferent versus sympathetic neuron to peripheral opioid analgesia. *The Journal of Pharmacology and Experimental Therapeutics*, 286: 1000-1006.
- Zöllner C, Mousa SA, Fischer O et al. (2008) Chronic morphine use does not induce peripheral tolerance in a rat model of inflammatory pain. *Journal of Clinical Investigation*, 118: 1065-1073.
- Zöllner C, Stein C. (2007) Opioids. In Stein C. (ed) *Analgesia. Handbook of Experimental Pharmacology*, 177, 31-63.

Chapter 14: Publications list

- Zeppetella G, Paul J, Ribeiro MDC. (2003) Analgesic efficacy of morphine applied topically to painful ulcers. *Journal of Pain and Symptom Management*, 26: 555-558.
- Ribeiro MD, Joel SP, Zeppetella G. (2004) The bioavailability of morphine applied topically to cutaneous ulcers. *Journal of Pain and Symptom Management*, 27: 434-439
- Zeppetella G, Joel SPJ, Ribeiro MDC. (2005) Stability of morphine sulphate and diamorphine hydrochloride in Intrasisite gel. *Palliative Medicine*, 19: 131-136.
- Zeppetella G, Ribeiro MDC. (2005) Morphine in Intrasisite Gel applied topically to painful ulcers. *Journal of Pain and Symptom Management*, 29: 118-119.

Original Article

Analgesic Efficacy of Morphine Applied Topically to Painful Ulcers

Giovambattista Zeppetella, MRCP, James Paul, MRCP,
and Maria D.C. Ribeiro, MRCP

*St. Joseph's Hospice (G.Z., J.P., M.D.C.R.), Barts and the London NHS Trust (G.Z., M.D.C.R.),
and University of London (M.D.C.R.), London, United Kingdom*

Abstract

The analgesic effects of morphine applied topically to painful ulcers was assessed in a randomized, double-blind, placebo-controlled, crossover pilot study of five patients with painful sacral sores. Patients were treated for two days with either 10 mg morphine sulfate or placebo (water for injection) applied topically to the ulcer. After a two-day wash-out period, patients were crossed over for a further two days of the alternative treatment. Patients were asked to rate analgesia using a visual analogue scale (VAS) and to document any local or systemic adverse effects. All patients reported lower VAS scores with morphine compared to placebo and no local or systemic adverse events attributable to morphine were noted by either patients or nursing staff. This pilot study suggests that morphine applied topically is an effective method of producing local analgesia, well tolerated by patients, and not associated with systemic adverse effects. J Pain Symptom Manage 2003;25:555–558. © 2003 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.

Key Words

Topical opioids, morphine, palliative care, pressure sore

Introduction

Pressure sores are a common clinical problem, occurring in up to 10% of hospital inpatients¹ and approximately 26% of hospice admissions.² Pressure sores are frequently associated with physical, emotional, and financial issues.³ Pain from pressure sores can be extremely difficult to treat, and usually is only partially responsive to conventional systemic analgesics. The ideal method of achieving

relief is healing of the ulcer. This, however, takes considerable time and, in the palliative care setting, is often never achieved.

There has been some interest in the use of morphine applied topically to painful ulcers in the palliative care setting. The potential advantage is that by producing a local analgesic effect, systemic medication can be reduced or avoided, and, consequently, there is less chance of systemic adverse effects. All classes of opioid receptors have now been demonstrated on peripheral nerve terminals, and are similar to the population of receptors found in the central nervous system.⁴ Opioid receptors are not evident in normal tissue but become detectable within minutes to hours after the start of inflammation, following increased production within

Address reprint requests to: Giovambattista Zeppetella, MRCP, St. Joseph's Hospice, Mare Street, London E8 4SA, United Kingdom.

Accepted for publication: November 2, 2002.

© 2003 U.S. Cancer Pain Relief Committee
Published by Elsevier Inc. All rights reserved.

0885-3924/03/\$—see front matter
doi:10.1016/S0885-3924(03)00146-5

the dorsal root ganglion and axonal transportation towards the nerve terminals.⁵

Several case studies have been published reporting the use of topical morphine for painful ulcers,⁶⁻⁹ and good analgesia has been described in the majority of cases. We report on a randomized, double-blind, placebo-controlled, crossover pilot study examining the analgesic effects of morphine applied topically to painful ulcers.

Methods

Hospice inpatients were entered into the study. Patients were eligible if they had a painful ulcer, which was not infected or covered by necrotic tissue and was suitable for once daily treatment with Intrasisite gel. Patients had to be capable of completing visual analogue scale (VAS) scores, and were receiving a stable analgesic regimen for at least 48 hours. For the purpose of the study, if the patient had ulcers on more than one site, only one site was chosen.

Following written informed consent, and using a table of random numbers, patients were randomly assigned to receive either morphine (morphine sulfate injection 10 mg/ml in 8 g Intrasisite gel) or placebo (water for injection 1 ml in 8 g Intrasisite gel). The person obtaining consent was blinded to the randomization sequence. Treatment was applied once daily (in the morning) after which the ulcer was covered with a Tegaderm dressing. Patients were treated for two days followed by a two-day washout period, after which they were crossed over to the alternative treatment. During the six-day study period, no changes were allowed in regularly scheduled analgesia; "rescue" analgesia was available in the usual way.

Patients were asked to assess the analgesic effects of each treatment arm by completing a 100-mm VAS score (no pain to unbearable

pain) twice daily. The average VAS scores for the treatment arms for each patient were compared using a Wilcoxon rank test. Patients and nursing staff also recorded any local or systemic adverse effects experienced during the course of the study. Ethical approval for the study was obtained from the local ethics committee.

Results

Subjects

Five patients with advanced malignant disease were recruited for this pilot study and randomized to order of treatment. All patients had painful sacral pressure sores ranging from 4.5 to 14 cm² (Table 1). Most patients were already using a regularly scheduled opioid for analgesia; one patient was using a nonsteroidal anti-inflammatory drug.

Efficacy Measures

Patients completed VAS scores twice daily, morning and afternoon (Table 2). The mean (\pm SD) VAS score for all patients was 47 ± 11 mm during placebo and 15 ± 11 mm during morphine. For each of the five patients, the average VAS scores for the two treatment arms was compared using the Wilcoxon rank test and found to be significant ($P < 0.01$). There was no difference in the patients' use of rescue medication during the two treatment arms.

Adverse Events

Most patients reported local symptoms associated with the ulcer. Patients 2, 4, and 5 reported localized discomfort while treated with placebo but not with morphine, and patients 1 and 3 noted itching, burning, and discomfort during treatment with both morphine and placebo. None of the local adverse effects appeared specifically attributable to morphine and no systemic adverse effects were documented by either patients or nursing staff.

Table 1
Patient Characteristics

Patient	1	2	3	4	5
Sex	Male	Female	Male	Female	Male
Age	80	87	78	62	81
Primary cancer	Lung	Pancreas	Prostate	Lung	Mesothelioma
Ulcer area (cm ²)	4.5	8	7.5	8.25	14
Stirling score	2	2.4	2.3	2.3	2.4
Scheduled analgesia	Morphine 2.5 mg 4 hourly	Morphine 20 mg 12 hourly	Diclofenac 50 mg 8 hourly	Extended-release morphine 30 mg 12 hourly	Extended-release morphine 30 mg 12 hourly

Table 2
Patient Characteristics and VAS Scores (mm)
Following Morphine and Placebo
Administered Topically to Painful Ulcers

Patient ^a	1	2	3	4	5
Placebo VAS Scores					
Day 1 morning	20	10	35	50	80
Day 1 afternoon	50	50	25	80	80
Day 2 morning	20	50	35	0	70
Day 2 afternoon	80	70	38	70	25
Mean	43	45	33	50	64
Morphine VAS Scores					
Day 1 morning	20	20	25	40	10
Day 1 afternoon	0	0	10	80	20
Day 2 morning	0	10	0	0	10
Day 2 afternoon	0	20	0	10	15
Mean	5	13	9	33	14

^aPatients 1 and 4 received placebo first; Patients 2, 3 and 5 received morphine first.

Discussion

This pilot study found that patients with painful pressure sores found morphine to be a more effective analgesic than placebo. Furthermore, morphine was generally well tolerated by patients, and although local reactions were described during the study, these were mild and probably not related to morphine. No systemic adverse effects were reported. These findings are consistent with the positive results of previous studies.

VAS scores varied considerably during the course of the study. Patient 3, for example, appeared pain-free in the morning of day 2 while on placebo, yet that afternoon was in severe pain. This is not totally unexpected as patients with cancer commonly report that pain intensity varies during the course of the day. Such variations may complicate assessment and measuring multiple VAS scores (worst pain, least pain, and average pain over the preceding 24 hours) may be necessary. The potential variation in pain intensity also underlines the potential value of a local treatment, as if pain spontaneously subsides systemic adverse effects would not be problematic.

Some patients appeared to respond better than others. Patients 1 and 3, for example, were pain-free on day 2 of morphine treatment, which may imply that the treatment is effective but did not have an immediate onset. Patient 5, however, appeared to benefit from placebo, as VAS scores fell from 80 mm to 25 mm in the 2-day period, whereas the VAS scores

during morphine, although low, showed no improvement.

Limited conclusions can be drawn from this pilot study, not only because of the small number of patients but also because a single dose was used. It is possible that patients responding less favorably may benefit from an increased dose of morphine. A dose titration study would be necessary to explore this further. Interestingly, patient 5 had the largest ulcer (three times larger than patient 1), and although one could assume that larger ulcers require higher analgesic doses, the actual situation is likely to be more complex and requires specific investigation.

There is now substantial evidence which supports that opioid receptors are present in peripheral sensory nerves and that they are activated by either endogenous or exogenous opioids. This possibility could allow us to provide local analgesia for painful ulcers, thus minimizing systemic adverse effects. No systemic adverse effects were reported by patients (including patient 3, who was opioid-naïve); this could support a local mode of action. A pharmacokinetic evaluation measuring serum morphine and its metabolites following topical administration would be required to support a local mode of action.

At present, it is unclear whether morphine (and other opioids) is stable or metabolized while in contact with painful ulcers. Diamorphine, which is also reportedly effective for painful ulcers, is generally considered to be devoid of intrinsic analgesic activity¹⁰ and requires de-acetylation to become active, although a specific diamorphine receptor may exist.¹¹ If opioid metabolism in peripheral tissues is important, then local factors such as blood flow, infection, and presence of necrotic tissue could all influence the amount of analgesia produced by opioids applied topically. For this reason, ulcers with infection and necrotic tissue were excluded from this study.

Most studies describing the topical effects of morphine have mixed the opioid in Intrasisite gel, although there are anecdotal reports in which morphine (or diamorphine) has been mixed with flomazine or metronidazole gel. Intrasisite gel is a hydrogel designed for debridement of necrotic tissue;¹² it is also designed for wounds that are granulating and epithelializing. When in contact with the wound, Intrasisite

absorbs excess exudates and produces a moist environment at the surface of the wound. Although generally well tolerated, it is possible that the local symptoms described by patients 1 and 3 were due to Intrasisite gel. There are no data available currently describing the stability of morphine in Intrasisite gel.

Some studies have reported that analgesia may last much longer than the 4-hour action of systemically administered morphine.⁹ Although not examined in this study (as the dressing was changed daily), the two-day washout was intended to minimize any possible carry-over effect. A possible way of testing this would be to apply the two treatments and measure the "time to exit" for each, a method applied elsewhere.¹³ If analgesia does last for several days, this would increase the attractiveness of this treatment option, as it would be more convenient for the patient and help reduce nurse workload.

In summary, this randomized, double-blind, placebo-controlled, crossover pilot study is consistent with the previous open studies that have reported an analgesic effect when morphine has been applied topically to painful ulcers. The patient numbers are small and these data, therefore, should be interpreted cautiously. There remain, however, a number of unanswered questions. Is topical morphine better than placebo? Does morphine work locally or systemically? What is the recommended dose and is this dependent on the characteristics of the ulcer (e.g., etiology, size, presence of infection and/or necrotic tissue)? How quickly is analgesia achieved and for how long does it last? We are currently undertaking a larger randomized, placebo-controlled trial to explore these questions further.

Acknowledgments

We would like to thank Dr. Ian Back for his advice regarding the protocol for the study and

the staff at St. Joseph's Hospice for their ongoing help and support.

References

1. Cullum N, Deeks J, Sheldon TA, et al. Beds, mattresses and cushions for pressure sore prevention and treatment (Cochrane Review). In: The Cochrane Library, Issue 2. Oxford: Update Software, 2002.
2. Galvin J. An audit of pressure ulcer incidence in a palliative care setting. *International J Palliat Nurs* 2002;8:214-221.
3. Vohra RK, McCollun CN. Fortnightly review: pressure sores. *BMJ* 1994;309:853-857.
4. Stein C. The control of pain in peripheral tissues by opioids. *N Engl J Med* 1995;332:1685-1690.
5. Hassan AHS, Ableiter A, Stein C, Herz A. Inflammation of the rat paw enhances axonal transport of opioid receptors in sciatic nerve and increases their density in the inflamed tissue. *Neuroscience* 1993;55:185-195.
6. Back IN, Finlay I. Analgesic effect of topical opioids on painful skin ulcers. *J Pain Symptom Manage* 1995;10:493.
7. Krajnik M, Zylicz Z. Topical morphine for malignant cutaneous pain. *Palliat Med* 1997;11:325.
8. Twillman RK, Long TD, Cathers TA, Mueller DW. Treatment of painful skin ulcers with topical opioids. *J Pain Symptom Manage* 1999;17:288-292.
9. Krajnik M, Zylicz Z, Finlay I, et al. Potential uses of topical opioids in palliative care—report of 6 cases. *Pain* 1999;80:121-125.
10. Inturrisi CE, Max MB, Foley KM, et al. The pharmacokinetics of heroin in patients with chronic pain. *N Engl J Med* 1984;310:1213-1217.
11. Rossi GC, Brown GP, Leventhal L, et al. Novel receptor mechanism for heroin and morphine-6 beta-glucuronide. *Neurosci Lett* 1996;216:1-4.
12. Williams C. Intrasisite gel a hydrogel dressing. *Br J Nurs* 1994;3:843-846.
13. Galer BS, Rowbotham MC, Perander J, Friedman E. Topical lidocaine relieves postherpetic neuralgia more effectively than a vehicle topical patch: results of an enriched enrollment study. *Pain* 1999;80:533-538.

Original Article

The Bioavailability of Morphine Applied Topically to Cutaneous Ulcers

Maria D.C. Ribeiro, MRCP, Simon P. Joel, PhD,
and Giovambattista Zeppetella, MRCP

St Joseph's Hospice, Barts and the London NHS Trust, and University of London (M.D.C.R.), London; Medical Oncology Department (S.P.J.), St Bartholomew's Hospital, London; and St. Clare Hospice, and The Princess Alexandra Hospital NHS Trust (G.Z.), Hastingwood, Essex, United Kingdom

Abstract

A number of studies have reported the analgesic effect of morphine when applied topically to painful skin ulcers. It has been suggested that morphine may exert a local action, as opioid receptors have been demonstrated on peripheral nerve terminals. In this study, we investigated the bioavailability of topically applied morphine to cutaneous ulcers. Six hospice inpatients with skin ulcers were given morphine sulfate 10 mg in Intraspine gel topically and morphine sulfate 10 mg subcutaneously over 4 hours, at least 48 hours apart, in randomized order. Morphine, morphine-6-glucuronide (M6G), and morphine-3-glucuronide (M3G) were determined in plasma using a specific HPLC method. In five patients morphine and its metabolites were undetectable when applied topically. In one patient (with the largest ulcer), morphine and M6G were detected. The calculated morphine and M6G bioavailability in this patient were 20% and 21%, respectively. M3G was also detected but was below the lower limit of quantitation. When applied topically to ulcers, morphine was not absorbed in the majority of patients, suggesting any analgesic effect would be mediated locally rather than systemically. However, in ulcers with a large surface area, systemic absorption may occur. J Pain Symptom Manage 2004;27:434–439. © 2004 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.

Key Words

Skin ulcers, topical morphine, bioavailability, morphine glucuronides, Intraspine gel, palliative care

Introduction

There is a growing body of experimental evidence suggesting that peripheral opioid receptors are activated by inflammatory changes in

tissue and that endogenous opioids may play a part in modulating the inflammatory process.¹ Clinical trials of intra-articular morphine following arthroscopic procedures have demonstrated an analgesic effect that is not dependent on systemic absorption of the drug.²

Several case studies describe the application of topical morphine to painful ulcers and demonstrate good (and relatively long-acting) analgesia in the majority of cases, with minimal

Address reprint requests to: Giovambattista Zeppetella, MRCP, St. Clare Hospice, Hastingwood Road, Hastingwood, Essex CM17 9JX, United Kingdom.

Accepted for publication: September 29, 2003.

© 2004 U.S. Cancer Pain Relief Committee
Published by Elsevier Inc. All rights reserved.

0885-3924/04/\$—see front matter
doi:10.1016/j.jpainsymman.2003.09.011

adverse effects.³⁻⁹ Pain from malignant and non-malignant cutaneous ulcers can be extremely difficult to treat and is often poorly controlled with systemic analgesics. A locally-acting analgesic would be advantageous in these patients, as it could allow systemic medication to be reduced and/or avoided, resulting in fewer systemic adverse effects.

Several opioids have been applied topically to ulcers, the most common of which is morphine (usually applied in Intrasisite gel), although other opioids, including diamorphine and fentanyl, have been used. Despite the increased use of topical opioids, there are no pharmacokinetic studies evaluating this route in palliative care patients. We report on the bioavailability of morphine and its metabolites, morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G), following the topical application of morphine sulfate mixed in Intrasisite gel to skin ulcers in hospice inpatients.

Methods

Six adult hospice patients were recruited into the study. Patients were eligible if they had skin ulcers (larger than 2 cm in diameter and 0.5 cm in depth) that were not infected or covered with necrotic tissue. Patients were required to be morphine, codeine, diamorphine or hydromorphone naive; fentanyl and tramadol were the only opioids permitted, as they do not interfere with the HPLC assay for morphine. Following written informed consent, patients received either morphine sulfate in Intrasisite gel applied topically to their ulcer or morphine sulfate administered subcutaneously over four hours, followed by the alternate treatment (topical or subcutaneous); the two treatments were separated by a washout period of one day. The order of treatments was randomized. This study was approved by the local ethics committee.

The topical morphine mixture was prepared by thoroughly mixing morphine sulfate injection BP 10 mg (Celltech Pharmaceuticals, Berkshire, UK) with Intrasisite gel 8 g (Smith & Nephew Healthcare Ltd, Middlesex, UK) in a sterile galipot; this dose of morphine was chosen as it is commonly used in clinical practice. The ulcer was first cleaned with sterile water, after which the morphine mixture was applied directly to the wound and then covered

with a tegaderm dressing. The opioid was kept in contact with the wound for 24 hours. Venous blood samples were taken from an indwelling cannula immediately prior to the application of morphine, and then at 1, 2, 4, 6, 8, 10, 12, and 24 hours afterwards.

The subcutaneous morphine infusion was prepared by diluting morphine sulfate 10 mg in water for injection to a volume of 10 mL in a plastic syringe. The syringe was then attached to a syringe driver (Graseby MS16a) and connected to an infusion set with the butterfly needle inserted in the upper forearm. The infusion set was primed with the morphine solution and the whole amount delivered over 4 hours. Venous blood samples were collected immediately prior to starting the infusion and then at 1, 2, 4, 6, 8, 10, and 12 hours after commencement.

All blood samples were separated by centrifugation (1000g for 10 minutes) within 30 minutes of collection and the plasma then stored at -40°C until analysis.

Pharmacokinetics Analysis

Morphine, M3G, and M6G were analyzed using a previously reported method,¹⁰ involving sample clean-up using C₈ cartridges (1 cc/100 mg Varian, Anachem, Luton, Beds) followed by reverse-phase HPLC with electrochemical and fluorescence detection. Extraction cartridges were conditioned with methanol (1.5 mL), 10 mM sodium dihydrogen phosphate, pH 2.1 with 10% acetonitrile (1.0 mL) and water (1.5 mL). Plasma (0.75 mL) was buffered with 500 mM ammonium sulfate, pH 9.3 (2.25 mL), and 2.5 mL of this mixture loaded onto the cartridge. The cartridge was then washed with 5 mM ammonium sulfate, pH 9.3 (5.0 mL), and water (0.2 mL). Morphine and its metabolites were eluted with 10 mM sodium dihydrogen orthophosphate pH 2.10 with 10% acetonitrile (0.80 mL).

Separation was achieved using an Apex 5 μ C₁₈ column (Jones Chromatography, Hengoed, Wales) fitted with a 2-cm Apex ODS 10 μ m precolumn. The mobile phase was 10 mM sodium dihydrogen phosphate, 1 mM sodium dodecyl sulfate, pH 2.1, with 25% acetonitrile. Morphine and M6G were detected by electrochemical detection and M3G by fluorescence detection. Approximate retention times for M3G, M6G, and morphine were 4, 5.5, and 10

minutes respectively, with lower limits of quantitation (LLQ) of 3 nM/L (1.1 ng/mL) for morphine, 2 nM/L (1 ng/mL) for M6G, and 40 nM/L (20 ng/mL) for M3G. Between-run variability for this assay at 100, 800, and 3500 nM/L M3G and 10, 80, and 350 nM/L morphine and M6G is <10%.

Pharmacokinetic parameters for morphine, M3G, and M6G were derived using non-compartmental methods in Kinetica (Innaphase Corp, Philadelphia, PA). The area under the concentration time curve (AUC) was calculated using the trapezoidal method as the sum of linear areas up to the maximum concentration and logarithmic areas from C_{\max} to the last time point (t_n). AUC was extrapolated out to infinity using the concentration at the last time point and the elimination rate constant (λ_z). C_{\max} and t_{\max} were the measured values. The elimination half-life was calculated as $0.693/\lambda_z$, the apparent clearance (CL) as dose divided by $AUC_{0-\infty}$ and the apparent volume of distribution as dose divided by the product of $AUC_{0-\infty} \times \lambda_z$. The bioavailability of morphine, and apparent bioavailability of M3G and M6G, after topical morphine were calculated as $AUC_{0-\infty, \text{TOPICAL}}/AUC_{0-\infty, \text{INFUSION}} \times 100$. Deconvolution analysis was performed within Kinetica using a model independent method (numerical deconvolution) to analyze absorption profiles. The results of this analysis are presented as percent of dose absorbed against time.

Results

Patients

Three male and three female hospice inpatients entered the study (Table 1).

The mean (range) surface area of the ulcers was 20.4 cm² (4.5–60 cm²); one ulcer was of

malignant etiology (patient 4), whereas the remainder were benign. Morphine, M6G, and M3G were below the lower limit of quantitation (<LLQ) in all samples prior to the administration of subcutaneous or topical morphine.

Subcutaneous Morphine

Mean plasma concentrations of morphine, M6G, and M3G in all six patients after subcutaneous morphine are shown in Figure 1. Morphine was detected in the first post-treatment sample (1 hour) in all patients and was still detectable in four patients at 12 hours. Peak morphine concentration was measured at 4 hours in 5 patients and at 2 hours in the remaining patient (56.5 nmol/L at 2 hours vs. 50.0 nmol/L at 4 hours). M6G was first detected at 1 hour in five patients and at 2 hours in one, and was still detectable in all patients at 12 hours. M3G was detected at 1 hour in one patient, 2 hours in four, and 3 hours in the remaining one. As with M6G, M3G remained detectable in all patients at 12 hours. Peak metabolite concentrations occurred between 4 and 8 hours (median t_{\max} 4 hours for M6G and 4.5 hours for M3G). Pharmacokinetic parameters for morphine, M6G, and M3G are shown in Table 2.

Topical Morphine

Morphine, M3G, and M6G were detected in the plasma of only one patient (patient 6) after topical application of morphine sulfate (Figure 2). This patient had the largest ulcer (60 cm²) compared to an average of 12.8 cm² in the other 5 patients. Both morphine and M6G were first detected at 1 hour, were still detectable at 12 hours but were <LLQ by 24 hours; the deconvolution analysis suggests that most of the topical dose was absorbed during the first hour, with relatively little further absorption thereafter.

Table 1
Patient and Ulcer Characteristics

Patient	Sex	Age	Diagnosis	Ulcer Size (cm ²)	Analgesia
1	Male	87	Ca colon	13	Paracetamol (acetaminophen) 1g prn
2	Male	61	Multiple sclerosis	9	Paracetamol 1g prn
3	Male	80	Ca prostate	5	Fentanyl-TTS 25 µg/h, diclofenac 50mg tds, paracetamol 1g qds
4	Female	73	Ca breast	23	Tramadol 100mg tds, ibuprofen 400mg tds
5	Female	70	COPD	14	None
6	Male	67	Ca lung	60	Paracetamol 1g qds, tramadol 200mg bd

COPD = Chronic obstructive pulmonary disease.

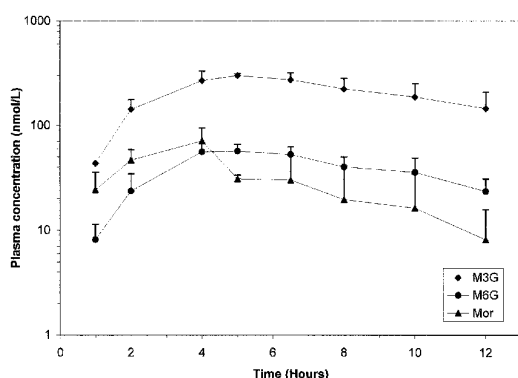


Fig. 1. Plasma morphine, M6G, and M3G concentration in 6 patients after 10 mg subcutaneous morphine infused over 4 hours (mean \pm SD).

(Figure 3). Morphine C_{\max} was in the first post-treatment sample (1 hour), whereas M6G C_{\max} was at 4 hours. Trace amounts of M3G, below the LLQ, were detected between 4 and 10 hours. Pharmacokinetic parameters for morphine and M6G are shown in Table 2, with bioavailabilities of 19.6% and 20.5%, respectively.

Adverse Events

During the topical application of morphine, neither patients nor nursing staff reported any systemic or local adverse events. During subcutaneous administration of morphine, one patient (Patient 2) reported drowsiness.

Discussion

Many patients, both in the hospital and in the community, have painful skin ulcers, including approximately 26% of hospice inpatients.¹¹ These patients are particularly vulnerable, as risk factors such as advanced age, immobility, and malnutrition are common. It may be possible to treat cutaneous pain in these patients, with fewer of the usual opioid-related adverse effects, by using relatively small doses of opioids applied directly onto the ulcer.

The pharmacokinetics of morphine, M6G, and M3G have been described following oral, subcutaneous, and intravenous administration of morphine in healthy volunteers and patients. One volunteer study has described the pharmacokinetics of morphine hydrochloride in solution delivered from an occlusive reservoir applied to de-epithelialized skin.¹² The bioavailability of morphine from this route and formulation was 75%, with stable morphine concentrations maintained for 11 hours. To our knowledge, ours is the first pharmacokinetic evaluation of morphine sulfate applied topically to skin ulcers in patients with advanced disease.

The aim of this study was to determine whether morphine sulfate in Intrasisite gel was absorbed systemically when applied to ulcerated skin. In five of the six patients, morphine and its metabolites were undetectable, suggesting limited, if any, systemic absorption. In one patient, who had the largest pressure sore, morphine and M6G were detected, with a bioavailability of 20%. The majority of skin ulcers

Table 2
Pharmacokinetics of Morphine and Its Glucuronides Following Subcutaneous Administration of Morphine Sulfate (all patients) Pharmacokinetics of Morphine and M6G After Topical Morphine in Intrasisite Gel (Patient 6)

	Morphine	M6G	M3G
Subcutaneous morphine (n = 6)			
C_{\max} (nmol/L)	72.6 \pm 22.5	60.2 \pm 6.6	303 \pm 36
t_{\max} (hr)	4 (2-4)	4 (4-8)	4.5 (4-8)
AUC ₀₋₁₂ (nmol/L.hr)	326 \pm 90	450 \pm 88	2339 \pm 262
AUC ₀₋₁₂ (nmol/L.hr)	356 \pm 105	588 \pm 82	3652 \pm 850
Apparent CL (mL/min)	1295 \pm 267	—	—
Apparent V_d (L)	281 \pm 52	—	—
Elimination $t_{1/2}$ (hr)	2.5 \pm 0.3	4.8 \pm 0.9	6.5 \pm 2.6
Topical morphine (Patient 6 only)			
C_{\max} (nmol/L)	9.4	9.5	—
t_{\max} (hr)	1	4	—
AUC ₀₋₁₂ (nmol/L.hr)	56	82	—
Bioavailability % (AUC ₀₋₁₂)	19.6	20.5	—

Values are mean \pm SD except t_{\max} which is the median (range).

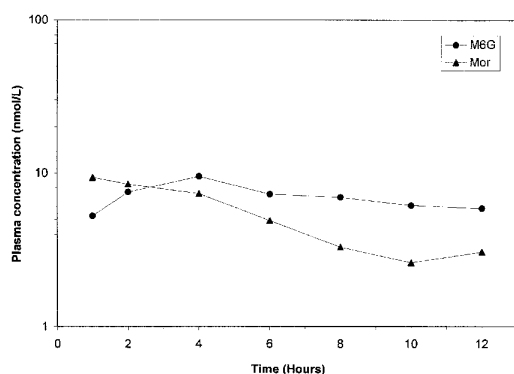


Fig. 2. Plasma morphine and M6G concentrations in patient 6 after 10 mg topical morphine in Intrasisite gel.

in clinical practice are smaller than that seen in patient 6, but it appears that if large ulcerated areas are treated topically, systemic absorption of morphine is likely. However, a bioavailability of 20% is unlikely to result in excessive systemic adverse effects given the relatively small daily dose of morphine applied topically and the fact that most patients with advanced disease are also likely to be on oral opioids.

The subcutaneous infusion route was included to determine the relative bioavailability of topical morphine. The estimate of total plasma morphine clearance after subcutaneous infusion in this study is slightly lower than that previously derived in healthy subjects¹³ (1295 vs. 2125 mL/min), resulting in an increased AUC_{0-t} (356 vs. 205 nmol/L·hr). This was likely due to the effects of age and ongoing disease in our study group.

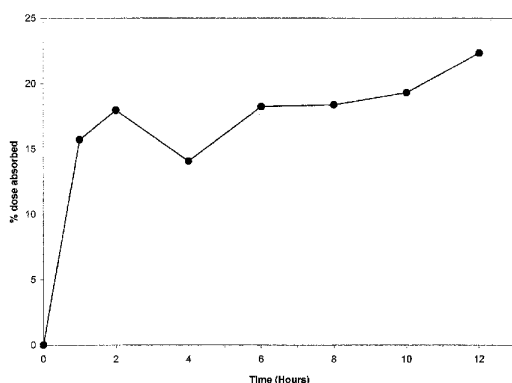


Fig. 3. Percentage dose absorbed against time for patient 6 after 10 mg topical morphine in Intrasisite gel.

Intrasisite gel, a ready-mixed hydrogel containing water, propylene glycol, and carboxy methyl cellulose, is widely used in the management of skin ulcers in the palliative care setting. When placed in contact with the wound, Intrasisite gel absorbs excess exudates and produces a moist environment at the surface of the wound. These fluid handling properties may influence the pharmacokinetics of opioids when they are mixed with Intrasisite gel and applied to skin ulcers. As hydrogels differ in the amounts of fluid they release or take up,¹⁴ the degree of absorption of drugs from these gels may also vary.

Several opioids have been applied topically to ulcers, including diamorphine, morphine, and fentanyl. We have investigated the bioavailability of morphine, as it appears to be the most commonly used in published reports. The advantages of morphine over other opioids are that it is widely available, is cheaper than most other opioid preparations, and is available in liquid form, which is easy to mix with a hydrophilic vehicle. Sampling of different parts of a morphine Intrasisite gel mix prior to commencing the study, prepared as described in the methods of our study, showed that the mixture had a fairly homogeneous morphine concentration (variability in concentration <20% for four samples). Also, the morphine/Intrasisite gel mixture has been shown not to degrade over time, whereas diamorphine mixed with Intrasisite gel showed some degradation to 6-monoacetylmorphine, and then morphine under the same conditions.¹⁵

In conclusion, when applied topically to ulcers in Intrasisite gel, morphine is not absorbed except when there is a large surface area. Reported analgesic effects after topical morphine are, therefore, likely to be mediated locally rather than systemically.

References

1. Stein C. The control of pain in peripheral tissues by opioids. *N Engl J Med* 1995;332:1685-1690.
2. McSwiney MM, Joshi GP, Kenny P, et al. Analgesia following arthroscopic surgery: a randomized, prospective, double-blind study. *Anesth Analg* 1992;74:822-826.
3. Back IN, Finlay I. Analgesic effect of topical opioids on painful skin ulcers. *J Pain Symptom Manage* 1995;10:493.

4. Krajnik M, Zylicz Z. Topical morphine for cutaneous cancer pain. *Palliat Med* 1997;11:325.
5. Twillman RK, Long TD, Cathers TA, et al. Treatment of painful skin ulcers with topical opioids. *J Pain Symptom Manage* 1999;17:288–292.
6. Krajnik M, Zylicz Z, Finlay I, et al. Potential uses of topical opioids in palliative care—report of 6 cases. *Pain* 1999;80:121–125.
7. Flock P, Gibbs L, Sykes N. Diamorphine-metronidazole gel effective for treatment of painful infected leg ulcers. *J Pain Symptom Manage* 2000;20:396–397.
8. Flock P. Pilot study to determine the effectiveness of diamorphine gel to control pressure ulcer. *J Pain Symptom Manage* 2003;25:547–554.
9. Zeppetella G, Paul J, Ribeiro MDC. Analgesic efficacy of morphine applied topically to painful ulcers. *J Pain Symptom Manage* 2003;25:555–558.
10. Joel S, Osborne RJ, Slevin M. An improved method for the simultaneous determination of morphine and its glucuronide metabolites. *J Chromatogr* 1988;430:394–399.
11. Galvin J. An audit of pressure ulcer incidence in a palliative care setting. *Int J Palliative Nursing* 2002;8:214–221.
12. Westerling D, Hoglund P, Lundin S, et al. Transdermal administration of morphine to healthy subjects. *Br J Clin Pharm* 1994;37:571–576.
13. Stuart-Harris R, Joel SP, McDonald P, et al. The pharmacokinetics of morphine and morphine glucuronide metabolites after subcutaneous bolus injection and subcutaneous infusion of morphine. *Br J Clin Pharmacol* 2000;49:207–214.
14. Thomas S, Hay P. Fluid handling properties of hydrogel dressings. *Ostomy Wound Manage* 1995;41:54–59.
15. Ribeiro MDC, Joel SP, Zeppetella G. Stability of morphine sulfate and diamorphine hydrochloride in Intrasis gel. Abstract. 8th Congress of the European Association for Palliative Care. The Hague, April 2003.

Stability of morphine sulphate and diamorphine hydrochloride in Intrasisite gel™

Giovambattista Zeppetella St. Clare Hospice, Hastingwood, Essex, **Simon P Joel** Medical Oncology Department, St. Bartholomew's Hospital, London and **Maria DC Ribeiro** Peace Hospice, Watford

Several studies have reported that opioids applied topically to painful ulcers produce an analgesic effect. It is unknown whether these opioids (usually mixed with hydrogels) are stable and, if so, for how long. We investigated the stability of morphine sulphate and diamorphine hydrochloride, each mixed with intrasisite gel at a concentration of 1.25 mg/mL. Samples were prepared in the laboratory and then stored in plastic containers in the dark, at room temperature, in conditions of normal day/night at room temperature, and at 4°C. Aliquots were collected from each container over a 28-day period and analysed using HPLC. No known degradation products were measured in the morphine–intrasisite gel mixture stored for up to 28 days, irrespective of the temperature and whether or not samples were exposed to light, suggesting that morphine remains stable. Diamorphine, breaks down to morphine and no other degradation products are measurable. *Palliative Medicine* 2005; **19**: 131–136

Key words: diamorphine; drug stability; intrasisite gel; morphine; skin ulcers; topical opioids

Introduction

Painful skin ulcers are a common problem in the palliative care setting; pressure sores, for example, have been shown to occur in approximately 26% of hospice admissions.¹ The ideal method of providing pain relief is healing of the ulcer but this is difficult in benign pressure sores and unlikely in malignant ulcers.

A number of studies have reported that opioids applied topically to painful ulcers can have an analgesic effect.^{2–9} Opioid receptors have been identified in peripheral tissues¹⁰ and it has been suggested that topically applied opioids may have a local action; bioavailability studies also suggest a local action.¹¹ The advantage of such a method is that local analgesia can be produced and systemic adverse effects avoided.

Morphine and diamorphine are the opioids most commonly used and usually mixed in intrasisite gel. Morphine degrades in aqueous solution to pseudomorphine (a morphine dimer formed at the C₇ position), morphine-N-oxide and possibly to apomorphine.¹² Diacetylmorphine hydrolyses to 6-monoacetylmorphine, and then to morphine,¹² with potential morphine degradation products formed thereafter.¹³ To date there is no information on whether either opioid is stable when mixed with intrasisite gel, and if so for how long. Mixtures, therefore, are prepared when required and

not in advance, which would be more convenient for patients and staff in both the inpatient and home setting. The aim of this study was to determine the stability of morphine sulphate in intrasisite gel and diamorphine hydrochloride in intrasisite gel over a 28-day period.

Methods

Approximately 8 grams of Intrasisite gel (Smith & Nephew Healthcare Ltd) containing morphine sulphate (Arum Pharmaceutical Ltd) or diamorphine hydrochloride (Arum Pharmaceutical Ltd) at a concentration of 1.25 mg/mL were prepared in the laboratory in 25 mL plastic containers and then mixed by stirring for 30 seconds with a sterile rod. Triplicate preparations of morphine or diacetylmorphine were then stored at 4°C in the dark, at room temperature in the dark, or at room temperature under day/night conditions (16 hours/8 hours, respectively) on the laboratory bench, approximately 8 feet from a window (but out of direct sunlight), and 6 feet from a fluorescent light that was illuminated during the hours 9 a.m.–7 p.m.

Aliquots (200–300 mg) were collected from each container after mixing with a sterile rod for 30 seconds on days 1 (baseline), 3, 5, 8, 11, 15, 21 and 28 for morphine and days 1, 3, 6, 8, 13, 17, 22 and 28 for diamorphine. Aliquots were weighed, diluted gravimetrically with buffer (high performance liquid chromatography (HPLC) mobile phase) by a factor of ten and mixed by rotation for one hour at room temperature. After

Address for correspondence: Giovambattista Zeppetella, BSc MRCP, Medical Director, Honorary Consultant Princess Alexandra Hospital NHS Trust, St. Clare Hospice, Hastingwood Road, Hastingwood, Essex CM17 9JX, UK.
E-mail: jzeppetella@stclare-hospice.co.uk

mixing samples further diluted 1:10 with HPLC mobile phase and then immediately analysed.

Quantitative standards for morphine and diacetylmorphine were also prepared at 1 mg/mL and diluted 1:10 with HPLC mobile phase prior to storage at -40°C . After defrosting, standards were further diluted 1:10 for analysis.

Morphine, diacetylmorphine and potential degradation products were quantified using a modification of a previously reported HPLC method.¹⁴ This could reliably resolve pseudomorphine and morphine-N-oxide (both McFarland Smith, Edinburgh, UK), apomorphine (Sigma Chemicals, Poole, Dorset, UK), morphine, diacetylmorphine (both local hospital pharmacy) and 6-monoacetylmorphine (6-MAM, sample for qualitative use provided by Dr Wynn Aherne, Institute of Cancer Research, Sutton, Surrey, UK). Separation was achieved using an Apex 5 μ C18 column (Jones Chromatography, Hengoed, Wales) fitted with a 2 cm Apex ODS 10 μ precolumn with a mobile phase comprising 10 mM sodium dihydrogen phosphate, 0.8 mM sodium dodecyl sulphate, pH 3.5, with 35% acetonitrile. All compounds were detected by UV absorbance at 287 nm. The concentration of 6-MAM was determined using the response factor for morphine. Recovery of morphine and diacetylmorphine from the intrasite gel was close to 100%. Measured concentration data was analysed using parametric analysis of variance in Minitab (Ohio, USA).

Results

Morphine sulphate

A total of 72 samples containing morphine sulphate were analysed. No evidence of pseudomorphine or morphine-N-oxide was found in any of the samples up to 28 days,

irrespective of the temperature and whether or not samples were exposed to light. The morphine concentration was most variable during the first five days of storage, after which recovered drug concentration stabilized (Figure 1). Including all the data in an analysis on variance found no effect of storage conditions on morphine concentration ($P=0.510$), but a significant time effect ($P=0.001$). A similar analysis including data from day eight onwards found no effect of storage time ($P=0.250$), suggesting the time effect was due to variability in recovered morphine concentration across the first five days when complete mixing on the samples might have been incomplete. After this initial mixing period the measured morphine concentration remained unchanged to 28 days.

Diamorphine hydrochloride

Analysis of the 72 diamorphine samples showed that diamorphine hydrochloride was degraded to 6-MAM, and then to morphine (ANOVA for storage time $P<0.001$). The rate and degree of degradation was related to the storage conditions (ANOVA <0.001 for diacetylmorphine, morphine and 6-MAM), with samples stored at room temperature showing a greater accumulation of 6-MAM with time than samples stored at 4°C (ANOVA $P<0.001$) (Figure 2). No morphine was detected in any sample stored at 4°C . Although the difference was small, recovered 6-MAM and morphine concentrations were consistently higher in samples stored at room temperature in the day/night light compared to dark (ANOVA $P=0.001$ for 6-MAM and morphine) (Figure 3). There was no difference in diamorphine concentration between these two storage conditions ($P=0.11$). By day 28 this resulted in 6-MAM and morphine concentrations of 0.367 ± 0.018 mg/mL and

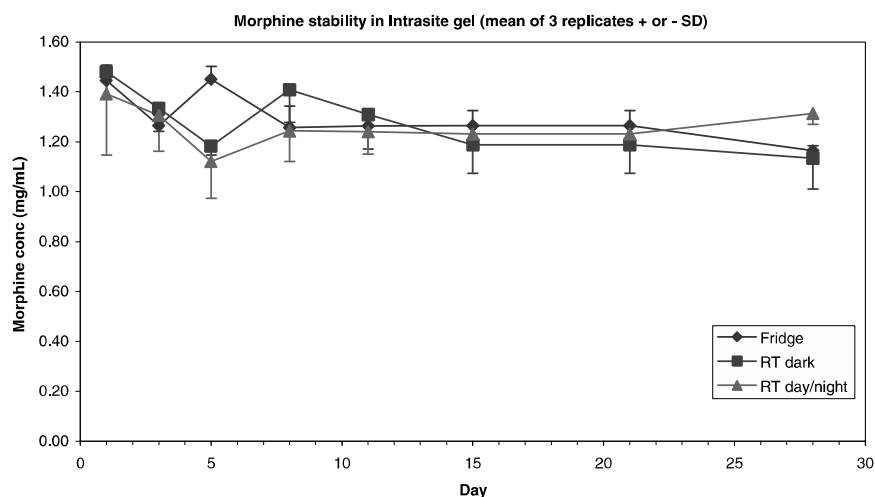


Figure 1 Stability of morphine sulphate in Intrasite gel™.

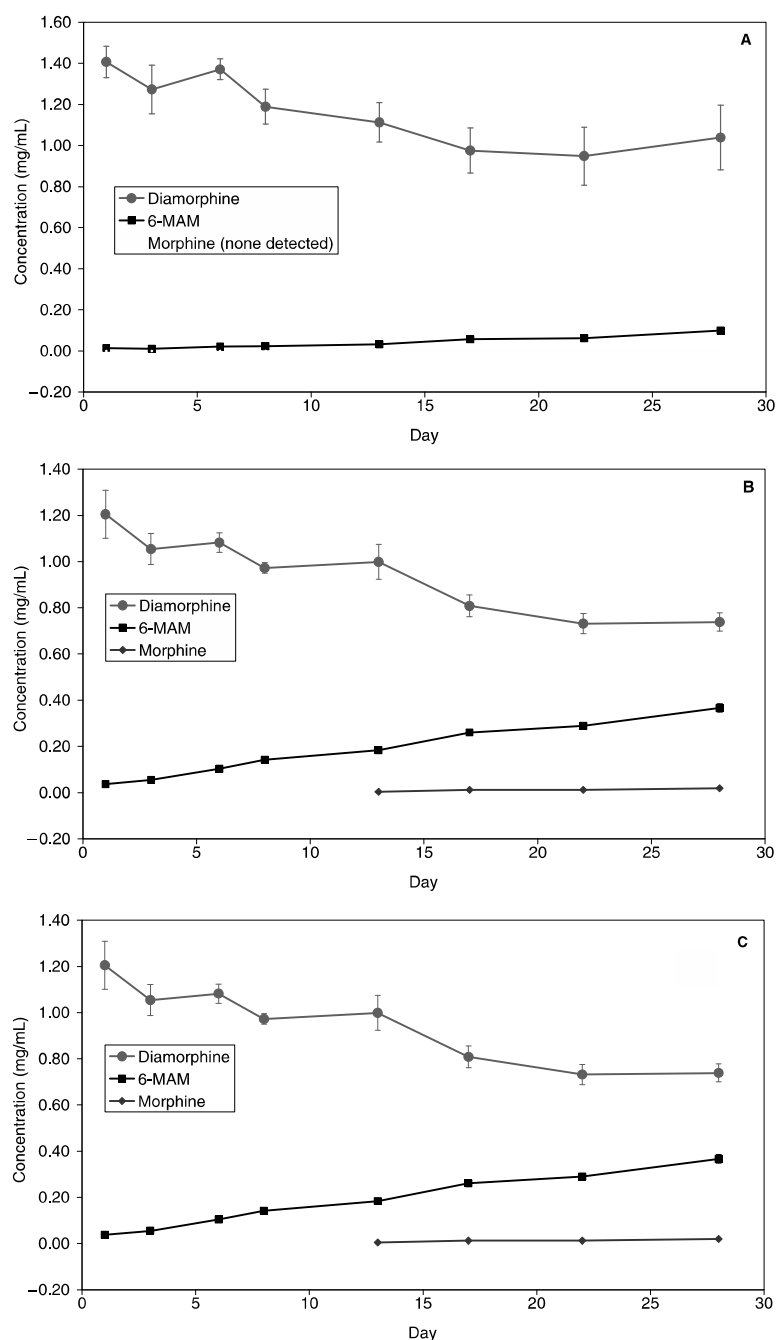


Figure 2 Stability of diamorphine hydrochloride in Intracite gelTM stored at 4°C (A), at room temperature in the dark (B) and dark/light (C).

0.019 ± 0.001 mg/mL, respectively, in samples stored at room temperature in the dark and 0.381 ± 0.007 and 0.021 ± 0.002 mg/mL for those exposed to light. No further morphine degradation products were found (Figure 4).

Discussion

Several studies have described an analgesic effect when opioids are applied topically to painful ulcers and that the analgesia is long lasting and locally specific. The

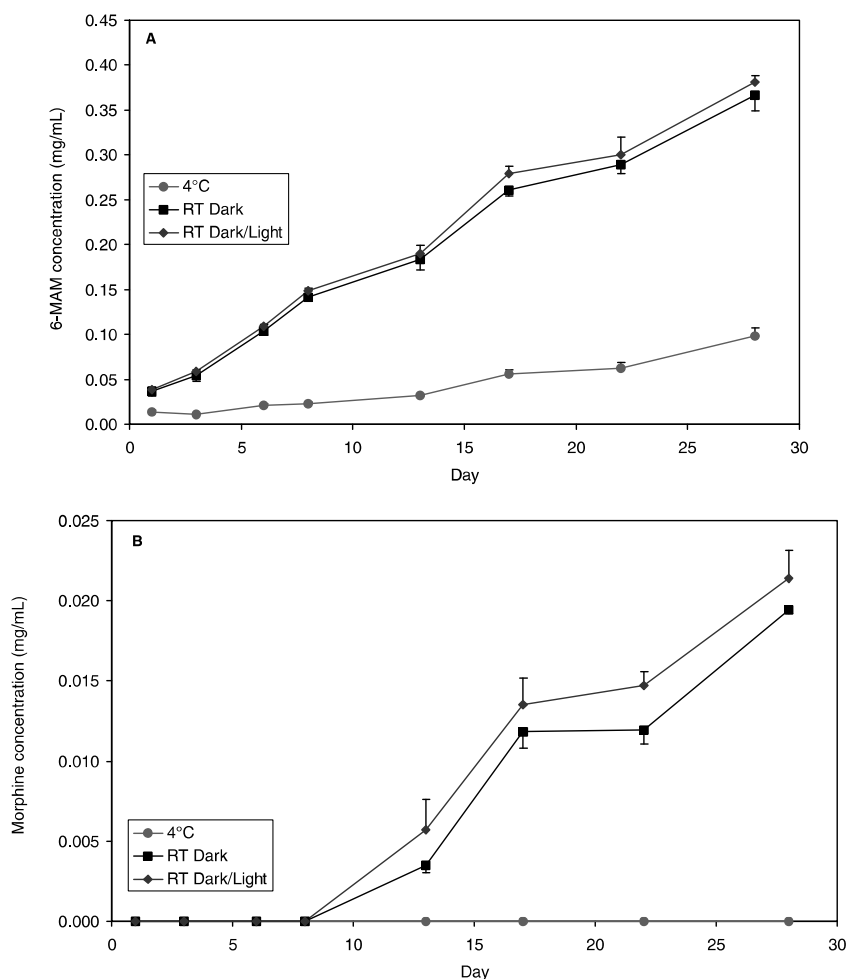


Figure 3 The appearance of 6-MAM (A) and morphine (B) from diamorphine in Intrasisite gel™ stored at different temperature and light conditions.

potential advantages of such a delivery system include optimizing opioid concentration at the site of pain, lower plasma opioid levels with potentially fewer adverse effects, and fewer drug interactions. There are a number of questions still to be answered before topical opioid therapy can become routine practice.¹⁵ In addition to confirmation of their efficacy there are practical issues, including whether or not opioids are stable in intrasisite gel. This information is important for pharmacists and clinicians to determine how to prepare the mixture, which is the preferred opioid, in what conditions should the mixture be stored, and what is the shelf life.

Previous studies have shown solutions of morphine sulphate for intravenous infusion appear to be relatively stable. In one study 0.04 mg/mL solutions retained more than 90% of their initial concentration of morphine sulphate when stored at 4°C for 23 days whether or not

they were protected by light.¹⁶ In our study some variation in morphine concentration was seen during the initial five days, probably because of incomplete mixing (a problem we had found in a preliminary study¹⁷), thereafter morphine appeared stable throughout the 28 days irrespective of the temperature and whether or not samples were exposed to light.

Diamorphine hydrochloride is preferred for topical administration in some units. It is generally considered to be a pro-drug, which in vivo is rapidly hydrolysed to active metabolites, although the presence of a novel mu receptor with which diamorphine, but not morphine, interact has been described.¹⁸ Aqueous solutions of diamorphine are less stable than solutions of morphine or codeine salts. Degradation of diamorphine has been shown to occur at different concentrations, and at different temperatures and the percentage fall is directly

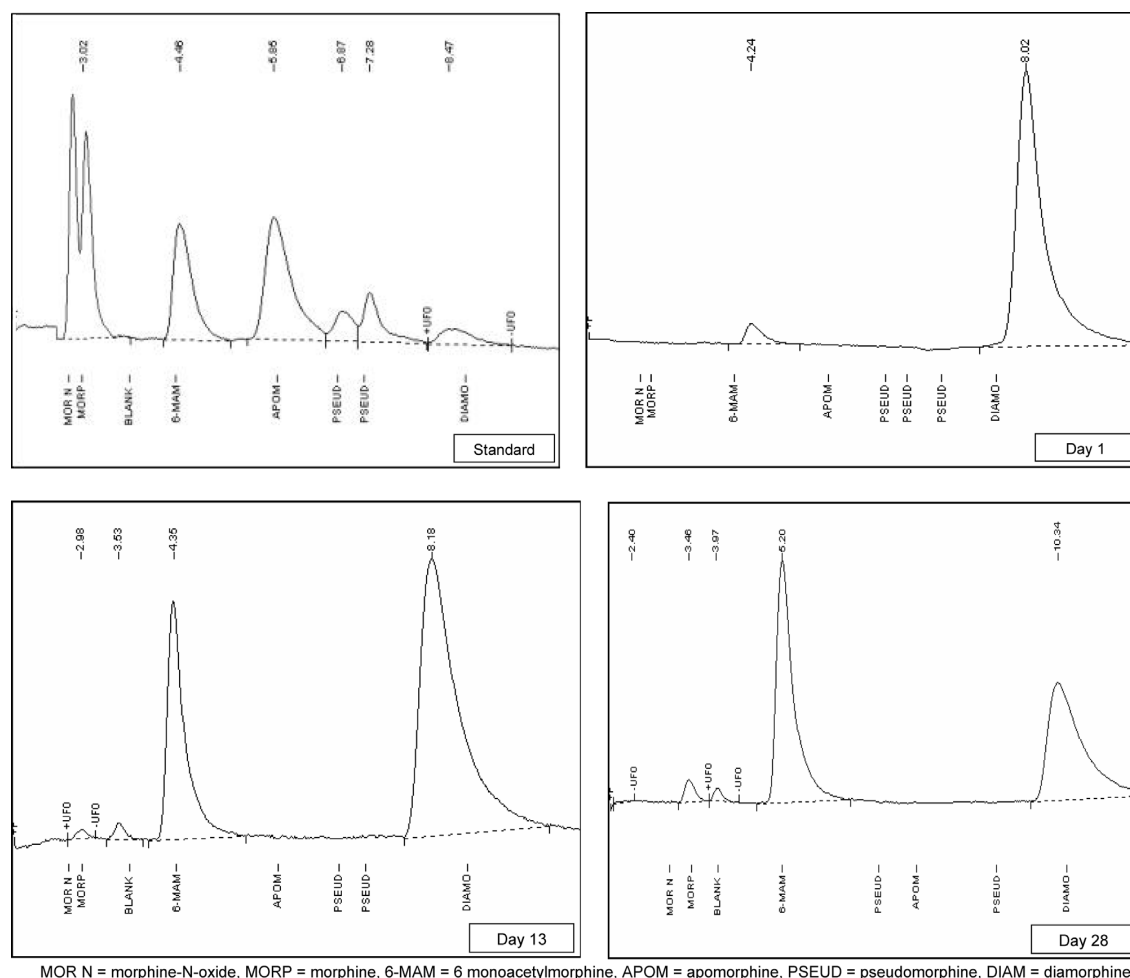


Figure 4 Chromatograms showing mixed mobile standard containing all compounds of interest, diamorphine Intrasisite gelTM stored at room temperature in the dark on day 1, 13 and 28 showing diacetylmorphine hydrolysis to 6-MAM, and then morphine. On days 13 and 28 the peak labelled blank was also present in the blank (mobile phase only) samples.

related to initial concentration and accompanied by a corresponding increase in 6-MAM and to a lesser extent morphine.¹⁹ This study also showed a degradation in diamorphine which was greater at room temperature compared to 4°C. This implies that diamorphine–intrasite mixtures should be stored at low temperature; although the degradation products are active metabolites in themselves. Indeed if diamorphine is solely a pro-drug it appears illogical to use it in this way, in addition to requiring metabolism to active metabolites it is not commonly available in all countries and according to UK prices is almost twice the cost of morphine.²⁰

Intrasite gel is a graft-T starch polymer hydrogel commonly used with opioids to topical application to painful wounds; hydrogels have also been used as carriers for antiseptics or antibiotics such as metronidazole.²¹

Intrasite is chemically stable and inert and usually a dressing for cavity wounds, extravasation injuries, venous ulcers and pressure sores, and acts by absorbing exudates, bacteria and toxins from the wound's surface, thereby preventing sloughing. The recommendation for storage is below 25°C in a dry place and once opened the gel should be used within seven days in order to avoid infection. Thus unless the opioid–intrasite gel mixture is prepared under sterile conditions the shelf life would be seven days (for infection control reasons) despite an opioid stability of at least 28 days.

There are guidelines regarding the conduct of studies designed to investigate the stability of drug preparations,²² with a value of $\pm 5\%$ of the prepared concentration generally taken as the limits of acceptance. As this was intended to be a limited stability study of the finished

product under storage conditions likely to be used in hospices, or by patients at home, where stability of longer than four weeks would not be required, the study endpoint was set at 28 days. Additionally, because of the difficulty in ensuring a homogeneous mix of the intrasite gel preparation described, particularly over the earlier time points, the standard $\pm 5\%$ change in drug concentration was not used as the indicator of stability. The criteria used as indicating loss of stability was the appearance of a known degradation product at $>5\%$ of the parent compound concentration.

In conclusion, the results of this study suggest that morphine remains stable when mixed with intrasite gel for up to 28 days and that diamorphine breaks down to morphine, which then remains stable. The practical implication of the study is that if opioids are mixed with intrasite gel under sterile conditions they can be then be stored for up to 28 days. If the mixture is not prepared under sterile conditions it should be used within seven days.

References

- Galvin J. An audit of pressure ulcer incidence in a palliative care setting. *International Journal of Palliative Nursing* 2002; **8**: 214–21.
- Back IN, Finlay I. Analgesic effect of topical opioids on painful skin ulcers. *J Pain Symptom Manage* 1995; **10**: 493.
- Krajnik M, Zylicz Z. Topical morphine for malignant cutaneous pain. *Palliat Med* 1997; **11**: 325.
- Krajnik M, Zylicz Z, Finlay I, Luczak J, van Sorge AA. Potential uses of topical opioids in palliative care – report of 6 cases. *Pain* 1999; **80**: 121–25.
- Twillman RK, Long TD, Cathers TA, Mueller DW. Treatment of painful skin ulcers with topical opioids. *J Pain Symptom Manage* 1999; **17**: 288–92.
- Flock P, Gibbs L, Sykes N. Diamorphine-intrasite gel effective for treatment of painful infected leg ulcers. *J Pain Symptom Manage* 2000; **20**: 396–97.
- Ballas SK. Treatment of painful sickle cell leg ulcers with topical opioids. *Blood* 2002; **99**: 1096.
- Flock P. Pilot study to determine the effectiveness of diamorphine gel to control pressure ulcer pain. *J Pain Symptom Manage* 2003; **25**: 547–54.
- Zeppetella G, Paul, J, Ribeiro MDC. Analgesic efficacy of morphine applied topically to painful ulcers. *J Pain Symptom Manage* 2003; **25**: 555–58.
- Stein C. The control of pain in peripheral tissues by opioids. *New Engl J Med* 1995; **332**: 1685–90.
- Ribeiro MDC, Joel SP, Zeppetella G. The bioavailability of morphine applied topically to cutaneous ulcers. *J Pain Symptom Manage* 2004; **27**: 434–39.
- Vermeire A, Remon JP. Stability and compatibility of morphine. *Int J Pharm* 1999; **187**: 17–51.
- Payne HAS, Tempest SM. The chemistry and pharmacy of diamorphine. In Scott DB ed. *Diamorphine*. Cambridge: Woodhead-Faulkner, 1988; 1–14.
- Joel SP, Osbourne R, Slevin M. An improved method for the simultaneous determination of morphine and its principle glucuronide metabolites. *J Chromatogr* 1988; **430**: 394–99.
- Zeppetella G. Topical opioids for painful skin ulcers: do they work? *Eur J Pall Care* 2004; **11**: 93–96.
- Vecchio M, Walker SE, Iazzetta J, Hardy BG. The stability of intravenous infusion solutions. *Can J Hosp Pharm* 1988; **41**: 5–9, 43.
- Ribeiro MDC, Zeppetella G, Joel SP. Stability of morphine sulphate and diamorphine hydrochloride in intrasite gel. 8th Congress of the European Association for Palliative Care, The Hague 2–5 April 2003.
- Rossi GC, Brown GP, Leventhal L, Yang K, Pasternak GW. Novel receptor mechanism for heroin and morphine-6 beta-glucuronide. *Neuroscience Letters* 1996; **216**: 1–4.
- Omar OA, Hoskin PJ, Johnston A, Hanks GW, Turner P. Diamorphine stability in aqueous solution for subcutaneous infusion. *J Pharm Pharmacol* 1989; **41**: 275–77.
- British National Formulary. Number 48; September 2004. British Medical Association and Royal Pharmaceutical Society: London, 2004.
- Thomas S, Hay NP. The antimicrobial properties of two metronidazole medicated dressings used to treat malodorous wounds. *Pharm J* 1991; **246**: 264–66.
- http://www.ich.org/UrlGrpServer.jsr?@_ID=276&@_TEMPLATE=254. Last accessed 5th November, 2004.

7. Folstein MF, Folstein SE, McHugh PR. "Minimal state." A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189-198.

Morphine in Intraspinal Gel Applied Topically to Painful Ulcers

To the Editor:

There have been a number of publications reporting the use of topical morphine for painful ulcers, including some randomized controlled studies.¹ We have reported the results of a pilot study,² following which we undertook a larger study. Although this study was terminated early because of administrative problems, the preliminary results are presented here, which may be informative.

Hospice inpatients with painful ulcers were randomly assigned to receive either morphine (morphine sulfate injection 10mg/ml in 8g Intraspinal gel) or placebo (water for injection 1 ml in 8g Intraspinal gel) topically to their ulcer. Patients were treated for two days followed by a two-day washout period after which they were crossed over to the alternative treatment. Patients assessed analgesia by completing a numerical rating score (NRS) daily. Patients, and nursing staff, also recorded any local or systemic

adverse effects experienced during the course of the study.

Twenty-one patients were recruited; five did not complete the study (deterioration (3), protocol violation (2)). Demographic details for the remaining 16 patients are shown in Table 1. The mean (\pm SD) NRS scores for patients pre-treatment, with morphine, and with placebo were 6.6 ± 1.6 , 2.8 ± 1.3 and 5.5 ± 1.9 , respectively (Table 2). Topically applied morphine produced significantly lower NRS scores compared to pre-treatment and placebo treatment ($P < 0.001$). Patients reported some local effects, such as itching, burning and discomfort, but none were specifically attributable to morphine; neither patients nor nursing staff documented any systemic adverse effects. Most patients (69%) preferred morphine to placebo and there was no difference in the patients' use of rescue medication during the two treatment arms.

This study is consistent with the previous reports describing an analgesic effect when morphine has been applied topically to painful malignant and benign ulcers. Furthermore, topically applied morphine appears to be safe and well tolerated by patients. The mechanism may be a local action as the bioavailability of topically applied morphine is low³ and the same dose appears effective across a range of oral opioid analgesics. Although this is the largest randomized, double-blind, placebo-controlled

Table 1
Patient Characteristics

Patient	Sex	Age	ECOG	Primary cancer	24-hr morphine equivalent (mg)	Ulcer characteristics		
						Size (cm ²)	Etiology	Sterling score
1	Female	72	3	Lung	25	6	Pressure	2.2
2	Male	78	3	Prostate	60	8.9	Pressure	2.3
3	Male	71	4	Lung	40	5.2	Pressure	2.3
4	Female	75	3	Esophagus	Nil	12.5	Pressure	3.1
5	Male	70	4	Lung	160	14	Pressure	3.2
6	Female	85	2	Lung	240	38	Pressure	2.3
7	Male	89	3	Stomach	80	5	Pressure	2.2
8	Female	92	4	Lung	60	14	Pressure	2.2
9	Male	79	3	Mesothelioma	20	22.4	Pressure	2.3
10	Male	82	3	Lung	Nil	9	Pressure	2.2
11	Male	71	3	Colon	20	15	Malignant	2.3
12	Female	80	3	Mesothelioma	120	8	Pressure	3.1
13	Male	65	3	Bladder	40	30	Malignant	3.2
14	Female	75	3	Esophagus	60	6.5	Pressure	2.2
15	Male	80	3	Anus	60	24	Malignant	2.2
16	Male	66	3	Pancreas	90	4.5	Pressure	3.1

Table 2
Patient Numerical Rating Scores Following Morphine and Placebo

Patient	First treatment	Numerical Rating Scores					Preference
		Baseline	Opioid Day 1	Opioid Day 2	Placebo Day 1	Placebo Day 2	
1	Morphine	6	4	3	8	7	Morphine
2	Morphine	6	2	3	4	6	Morphine
3	Placebo	9	6	4	5	3	Placebo
4	Placebo	7	4	2	9	6	Morphine
5	Placebo	5	3	1	4	5	Morphine
6	Placebo	6	4	3	8	8	Morphine
7	Morphine	8	2	1	7	9	Morphine
8	Placebo	5	5	4	4	7	None
9	Morphine	8	3	5	4	3	Placebo
10	Morphine	10	3	4	9	7	None
11	Morphine	6	2	1	4	5	Morphine
12	Morphine	4	3	2	3	3	None
13	Placebo	6	2	3	5	4	Morphine
14	Morphine	5	2	0	4	3	Morphine
15	Placebo	7	2	1	6	5	Morphine
16	Morphine	7	3	2	5	6	Morphine

study to date, the sample size is relatively small and larger studies are required to confirm these findings.

Giovambattista Zeppetella, BSc, MRCP
St. Clare Hospice
Hastingwood, United Kingdom

Maria D.C. Ribeiro, MRCP
Peace Hospice
Watford, United Kingdom

doi:10.1016/j.jpainsymman.2004.12.006

References

1. Zeppetella G. Topical morphine for painful ulcers. Does it work? *Eur J Pall Med* 2004;11:93–96.
2. Zeppetella G, Paul J, Ribeiro MDC. Analgesic efficacy of morphine applied topically to painful ulcers. *J Pain Symptom Manage* 2003;25:555–558.
3. Ribeiro MDC, Joel SP, Zeppetella G. The bioavailability of morphine applied topically to cutaneous ulcers. *J Pain Symptom Manage* 2004;27:434–439.

Re: Olanzapine-Induced Delirium

To the Editor:

In response to the letter by Morita and co-workers in a previous issue of this journal,¹ I would like to address several points regarding the treatment of emesis in advanced cancer, use of olanzapine as an antiemetic, and olanzapine-induced delirium.

Olanzapine is an atypical neuroleptic drug of the thienobenzodiazepine class that is structurally related to clozapine. Olanzapine is a selective monoaminergic antagonist with high-affinity binding to serotonin 5-HT_{2A}, 5-HT_{2C}, 5-HT₃, 5-HT₆, dopamine (D₁-D₄), and muscarinic, histaminergic, and α_1 -adrenergic receptors.² The approach to treating nausea and vomiting in advanced cancer may be based either on current understanding of the neuropharmacology of the emetic pathway or on empiric evidence (using various antiemetics without regard to the underlying mechanism).³ The second approach can be successful, especially if a broad-spectrum antiemetic is used. Either approach is valid, although a recent review suggests that approaching vomiting from an etiology-based approach may be more valid as well.³

In this patient, nausea and vomiting was attributed to radiation, opioids, and cachexia. The mechanism of radiation-induced nausea and vomiting is thought to be due to radiation-induced injury to the GI tract, with release of serotonin, stimulation of vagal afferents, and subsequent stimulation of the area postrema, nucleus tractus solitarius, dorsal motor nucleus of the vagus, and the central pattern generator leading to emesis, nausea, or both.⁴ The serotonin 5-HT₃ receptor subtype is the receptor involved in acute nausea and vomiting associated with cis-platinum chemotherapy.⁴

In the current case, older agents did not provide significant 5-HT₃ serotonin blocking activity, save for metoclopramide (which can block

Chapter 15: Appendices

- 15.1 The Oxford Quality Score
- 15.2 Scottish Intercollegiate Guidelines Network Grading levels of evidence for research
- 15.3 Waterlow Score Card
- 15.4 Classification of Eastern Co-operative Oncology Group Performance Status
- 15.5 Ethics approval for thesis related studies
- 15.6 Pilot efficacy study: Trial diary of patient number three to highlight problem with NRS scores
- 15.7 Extended efficacy study: Trial diary of patient number one
- 15.8 Patient bioavailability data following application of morphine to cutaneous ulcers

15.1. Oxford Quality Score

Oxford scale for quality scoring controlled trials

This is not the same as being asked to review a paper. It should not take more than 10 minutes to score a report and there are no right or wrong answers.

Please read the article and try to answer the following questions (see attached instructions):

- 1 Was the study described as randomised (this includes the use of words such as randomly, random and randomisation)?
- 2 Was the study described as double-blind?
- 3 Was there a description of withdrawals and drop outs?

Scoring the items:

Give a score of 1 point for each 'yes' and 0 points for each 'no'. There are no in-between marks.

Give 1 additional point if:

On question 1, the method of randomisation was described and it was appropriate (table of random numbers, computer generated, coin tossing, etc.)

and/or:

If on question 2 the method of double-blinding was described and it was appropriate (identical placebo, active placebo, dummy, etc.)

Deduct 1 point if:

On question 1, the method of randomisation was described and it was inappropriate (patients were allocated alternatively, or according to date of birth, hospital number, etc.)

and/or:

On question 2 the study was described as double-blind but the method of blinding was inappropriate (e.g., comparison of tablet vs. injection with no double dummy)

Advice on using the scale

1. Randomisation:

If the word randomised or any other related words such as random, randomly, or randomisation are used in the report, but the method of randomisation is not described, give a positive score to this item. A randomisation method will be regarded as appropriate if it allowed each patient to have the same chance of receiving each treatment and the investigators could not predict which treatment was next. Therefore methods of allocation using date of birth, date of admission, hospital numbers or alternation should not be regarded as appropriate.

2. Double-blinding:

A study must be regarded as double-blind if the word double-blind is used (even without description of the method) or if it is implied that neither the caregiver nor the patient could identify the treatment being assessed.

3. Withdrawals and drop outs:

Patients who were included in the study but did not complete the observation period or who were not included in the analysis must be described. The number and the reasons for withdrawal must be stated. If there are no withdrawals, it should be stated in the article. If there is no statement on withdrawals, this item must be given a negative score (0 points).

df

15.2: Levels of Evidence: Key to evidence statements used by the Scottish Intercollegiate Guidelines Network 2008

Level	Example
1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

15.3 Waterlow Score Card

WATERLOW PRESSURE ULCER PREVENTION/TREATMENT POLICY
RING SCORES IN TABLE, ADD TOTAL. MORE THAN 1 SCORE/CATEGORY CAN BE USED

BUILD/WEIGHT FOR HEIGHT	SKIN TYPE VISUAL RISK AREAS	SEX	AGE	MALNUTRITION SCREENING TOOL (MST) (Nutrition Vol.15, No.6 1999 - Australia)	
AVERAGE BMI = 20-24.9	HEALTHY	0	MALE	1	A - HAS PATIENT LOST WEIGHT RECENTLY
ABOVE AVERAGE BMI = 25-29.9	DRY	1	FEMALE	2	YES - GO TO B
OBESSE BMI > 30	OEDEMATOUS	1	14 - 49	1	NO - GO TO C
BELOW AVERAGE BMI < 20	CLAMMY, PYREXIA	1	50 - 64	2	UNSURE - GO TO C AND SCORE 2
BMI = $\frac{Wt(Kg)}{Ht(m)^2}$	DISCOLOURED	2	65 - 74	3	
	GRADE 1	2	75 - 80	4	C - PATIENT EATING POORLY OR LACK OF APPETITE
	BROKEN/SPOTS	3	81 +	5	'NO' = 0; 'YES' SCORE = 1
	GRADE 2-4	3			NUTRITION SCORE If > 2 refer for nutrition assessment / intervention
SPECIAL RISKS					
CONTINENCE	MOBILITY		TISSUE MALNUTRITION		
COMPLETE/CATHETERISED	0 FULLY RESTLESS/FIDGETY	0	8	DIABETES, MS, CVA	
URINE INCONT.	1 APATHETIC	1	8	MOTOR/SENSORY	
FAECAL INCONT.	2 RESTRICTED	2	5	PARAPLEGIA (MAX OF 6)	
URINARY + FAECAL INCONTINENCE	3 BEDBOUND e.g. TRACTION CHAIRBOUND e.g. WHEELCHAIR	3	5	MAJOR SURGERY or TRAUMA	
		4	5	ORTHOPAEDIC/SPINAL	
		5	2	ON TABLE > 2 HR#	
			1	ON TABLE > 6 HR#	
			MEDICATION - CYTOTOXICS, LONG TERM/HIGH DOSE STEROIDS, ANTI-INFLAMMATORY MAX OF 4		
# Scores can be discounted after 48 hours provided patient is recovering normally					
SCORE 10+ AT RISK 15+ HIGH RISK 20+ VERY HIGH RISK					

© J Waterlow 1985 Revised 2005*
Obtainable from the Nook, Stoke Road, Henlade TAUNTON TA3 5LX
* The 2005 revision incorporates the research undertaken by Queensland Health.

www.judy-waterlow.co.uk

REMEMBER TISSUE DAMAGE MAY START PRIOR TO ADMISSION. IN CASUALTY, A SEATED PATIENT IS AT RISK ASSESSMENT (See Over) IF THE PATIENT FALLS INTO ANY OF THE RISK CATEGORIES, THEN PREVENTATIVE NURSING IS REQUIRED A COMBINATION OF GOOD NURSING TECHNIQUES AND PREVENTATIVE AIDS WILL BE NECESSARY ALL ACTIONS MUST BE DOCUMENTED

PREVENTION PRESSURE REDUCING AIDS Special Mattress/beds: 10+ Overlays or specialist foam mattresses. 15+ Alternating pressure overlays, mattresses and bed systems. 20+ Bed systems: Fluidised bead, low air loss and alternating pressure mattresses. Note: Preventative aids cover a wide spectrum of specialist features. Efficacy should be judged, if possible, on the basis of independent evidence. No person should sit in a wheelchair without some form of cushioning. If nothing else is available - use the person's own pillow. (Consider infection risk) 10+ 100mm foam cushion 15+ Specialist Gel and/or foam cushion 20+ Specialised cushion, adjustable to individual person. Bed clothing: Avoid plastic draw sheets, inco pads and tightly tucked in sheet/sheet covers, especially when using specialist bed and mattress overlay systems. Use duvet - plus vapour permeable membrane.	Skin Care General hygiene, NO rubbing, cover with an appropriate dressing WOUND GUIDELINES Assessment odour, exudate, measure/photograph position WOUND CLASSIFICATION - EPUAP GRADE 1 Discolouration of intact skin not affected by light finger pressure (non-blanching erythema) This may be difficult to identify in darkly pigmented skin GRADE 2 Partial thickness skin loss or damage involving epidermis and/or dermis The pressure ulcer is superficial and presents clinically as an abrasion, blister or shallow crater GRADE 3 Full thickness skin loss involving damage of subcutaneous tissue but not extending to the underlying fascia The pressure ulcer presents clinically as a deep crater with or without undermining of adjacent tissue GRADE 4 Full thickness skin loss with extensive destruction and necrosis extending to underlying tissue. Dressing Guide Use Local dressings formulary and/or www.worldwidewounds IF TREATMENT IS REQUIRED, FIRST REMOVE PRESSURE
NURSING CARE General HAND WASHING, frequent changes of position, lying, sitting. Use of pillows. Pain Appropriate pain control Nutrition High protein, vitamins and minerals Patient Handling Correct lifting technique - hoists - monkey poles Transfer devices Patient Comfort Aids Real Sheepskin - bed cradle Operating Table Theatre/A&E Trolley 100mm(4ins) cover plus adequate protection	

15.4 Classification of Eastern Co-operative Oncology Group Performance Status

Score	Performance
0	Fully active, able to carry on all activities without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light and sedentary nature
2	Ambulatory and capable of all self care; confined to bed or chair 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair 50% or more of waking hours
4	Completely disabled; cannot carry on any self care; totally confined to bed or chair

15.5 Ethics approval for clinical studies



Mare Street, London E8 4SA
Tel: 020 8525 6000
Fax: 020 8533 0513
E-mail: info@stjh.org.uk
www.stjh.org.uk

Our Ref: MC/TJK

12 May 2006

Dr John Zeppetella
Medical Director
St Clare Hospice
Hastingwood Road
HASTINGWOOD
Essex CM17 9JX

Dear John

We are happy to confirm that the following research topics were approved by St Joseph's Hospice' Ethics and Research Committee:

1. Topical Morphine for Painful Ulcers – Pilot Study
2. Topical Morphine Pharmacokinetics
3. Stability of Morphine in an 'Intrasite Gel' Medium
4. Topical Morphine for Painful Ulcers – A Randomised Double Blind Placebo Controlled Trial

If there is anything further we can assist you with, please do not hesitate to contact us.

With kind regards,

Yours sincerely

Maura Cochrane
Assistant Director Patient Services (Quality)



Founded in 1905 under the care of the Sisters of Charity • Caring with Faith, Hope and Love

Charity registration No. 231323

15.6 Pilot efficacy study: Trial diary of patient number three

Patient Trial Diary



To be kept by patient or in patient's medical/nursing notes.

All questions about pain refer to the pain from **the ulcer** that we will be applying a special dressing to during this study. If you have pain from other sources please do not include this when answering these questions. It is the pain from the **skin ulcer** that we would like you tell us about.

If you would like help in filling out any part of this diary please ask a member of the ward staff.

Patient's Trial Number

3

Patient's Hospice Number

00/0265

Site of ulcer

SACRUM / BUTTOCKS

Day 1

9am On average how intense has the pain been from the ulcer in the previous 24 hours? (tick the appropriate box)

☐ No pain

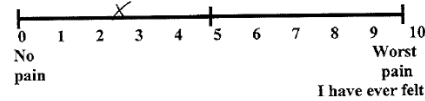
☒ Mild

☐ Moderate

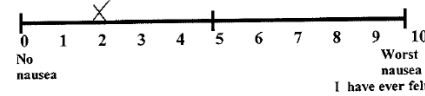
☐ Severe

☐ Excruciating/very severe

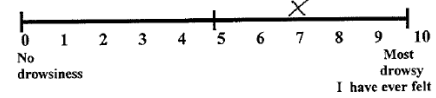
If you were to give a score of 0 – 10 for the average intensity of pain that you have experienced from the ulcer in the past 24 hours what score would you give? (place an X on the line below that corresponds with the score you give for the pain)



If you were to give a score from 0 – 10 for the average feeling of nausea that have experienced over the previous 24 hours what score would you give? (place an X on the line below to show the score you give)



If you were to give a score from 0 – 10 for the average degree of drowsiness (sleepiness) you felt yesterday from 9am to 9pm (ie normal waking hours), what score would you give? (place an X on the line below to show the score you give)



In the past 24 hours have you experienced any of the following at the ulcer site? (tick any relevant boxes)

- ☒ Itching
- ☒ Burning
- ☐ Irritation
- ☐ Discomfort other than pain

Day 1

5pm On average how intense has the pain been from the ulcer in the previous 8 hours? (tick the appropriate box)

☐ No pain

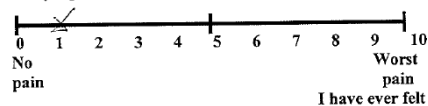
☒ Mild *day*

☐ Moderate

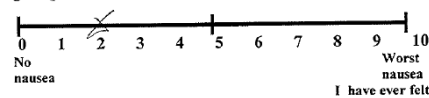
☐ Severe

☐ Excruciating/very severe

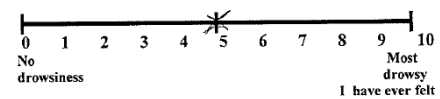
If you were to give a score of 0 – 10 for the average intensity of pain that you have experienced from the ulcer in the past 8 hours what score would you give? (place an X on the line below that corresponds with the score you give for the pain)



If you were to give a score from 0 – 10 for the average feeling of nausea that have experienced over the previous 8 hours what score would you give? (place an X on the line below to show the score you give)



If you were to give a score from 0 – 10 for the average degree of drowsiness (sleepiness) you have felt over the previous 8 hours, what score would you give? (place an X on the line below to show the score you give)



In the past 8 hours have you experienced any of the following at the ulcer site? (tick any relevant boxes)

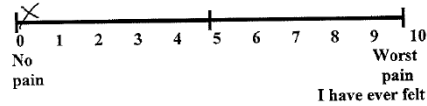
- ☒ Itching
- ☐ Burning
- ☐ Irritation
- ☐ Discomfort other than pain

Day 2

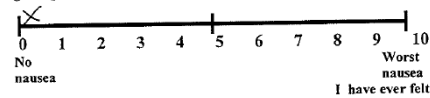
9am On average how intense has the pain been from the ulcer in the previous 8 hours? (tick the appropriate box)

- ☒ No pain
☐ Mild
☐ Moderate
☐ Severe
☐ Excruciating/very severe

If you were to give a score of 0 – 10 for the average intensity of pain that you have experienced from the ulcer in the past 8 hours what score would you give? (place an X on the line below that corresponds with the score you give for the pain)



If you were to give a score from 0 - 10 for the average feeling of nausea that you have experienced over the previous 8 hours what score would you give? (place an X on the line below to show the score you give)



In the past 8 hours have you experienced any of the following at the ulcer site? (tick any relevant boxes)

- ☒ Itching
☐ Burning
☐ Irritation
☒ Discomfort other than pain

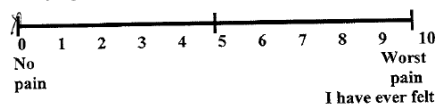
little

Day 2

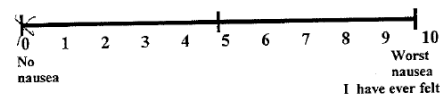
5pm On average how intense has the pain been from the ulcer in the previous 8 hours? (tick the appropriate box)

- ☒ No pain
☐ Mild
☐ Moderate
☐ Severe
☐ Excruciating/very severe

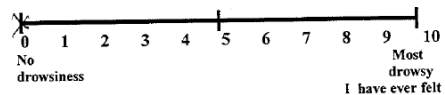
If you were to give a score of 0 – 10 for the average intensity of pain that you have experienced from the ulcer in the past 8 hours what score would you give? (place an X on the line below that corresponds with the score you give for the pain)



If you were to give a score from 0 - 10 for the average feeling of nausea that you have experienced over the previous 8 hours what score would you give? (place an X on the line below to show the score you give)



If you were to give a score from 0 – 10 for the average degree of drowsiness (sleepiness) you have felt over the previous 8 hours, what score would you give? (place an X on the line below to show the score you give)



In the past 8 hours have you experienced any of the following at the ulcer site? (tick any relevant boxes)

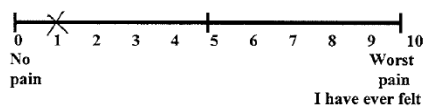
- ☒ Itching
☐ Burning
☐ Irritation
☐ Discomfort other than pain

Day 3

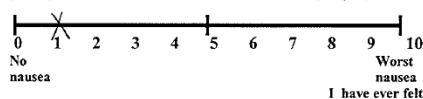
9am On average how intense has the pain been from **the ulcer** in the previous 8 hours? (tick the appropriate box)

- ☒ No pain
☐ Mild
☐ Moderate
☐ Severe
☐ Excruciating/very severe

If you were to give a score of 0 – 10 for the average intensity of pain that you have experienced **from the ulcer** in the past 8 hours what score would you give? (place an X on the line below that corresponds with the score you give for the pain)



If you were to give a score from 0 – 10 for the average feeling of nausea that have experienced over the previous 8 hours what score would you give? (place an X on the line below to show the score you give)



In the past 8 hours have you experienced any of the following at the **ulcer** site? (tick any relevant boxes)

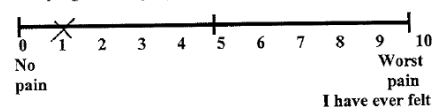
- ☐ Itching
☐ Burning
☐ Irritation
☐ Discomfort other than pain

Day 3

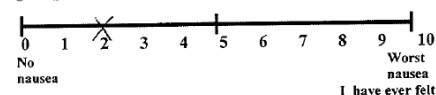
5pm On average how intense has the pain been from **the ulcer** in the previous 8 hours? (tick the appropriate box)

- ☒ No pain
☐ Mild
☐ Moderate
☐ Severe
☐ Excruciating/very severe

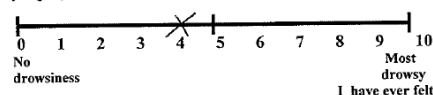
If you were to give a score of 0 – 10 for the average intensity of pain that you have experienced **from the ulcer** in the past 8 hours what score would you give? (place an X on the line below that corresponds with the score you give for the pain)



If you were to give a score from 0 – 10 for the average feeling of nausea that have experienced over the previous 8 hours what score would you give? (place an X on the line below to show the score you give)



If you were to give a score from 0 – 10 for the average degree of drowsiness (sleepiness) you have felt over the previous 8 hours, what score would you give? (place an X on the line below to show the score you give)



In the past 8 hours have you experienced any of the following at the **ulcer** site? (tick any relevant boxes)

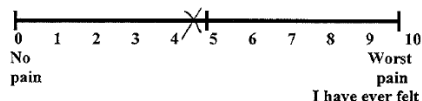
- ☐ Itching
☐ Burning
☐ Irritation
☐ Discomfort other than pain

Day 4

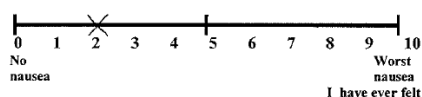
9am On average how intense has the pain been from the ulcer in the previous 8 hours? (tick the appropriate box)

- ☐ No pain
☐ Mild
☒ Moderate
☐ Severe
☐ Excruciating/very severe

If you were to give a score of 0 – 10 for the average intensity of pain that you have experienced from the ulcer in the past 8 hours what score would you give? (place an X on the line below that corresponds with the score you give for the pain)



If you were to give a score from 0 – 10 for the average feeling of nausea that have experienced over the previous 8 hours what score would you give? (place an X on the line below to show the score you give)



In the past 8 hours have you experienced any of the following at the ulcer site? (tick any relevant boxes)

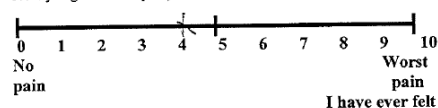
- ☐ Itching
☒ Burning
☐ Irritation
☐ Discomfort other than pain

Day 4

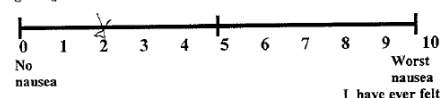
5pm On average how intense has the pain been from the ulcer in the previous 8 hours? (tick the appropriate box)

- ☐ No pain
☐ Mild
☒ Moderate
☐ Severe
☐ Excruciating/very severe

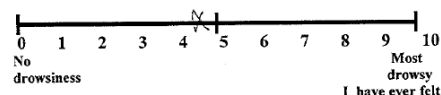
If you were to give a score of 0 – 10 for the average intensity of pain that you have experienced from the ulcer in the past 8 hours what score would you give? (place an X on the line below that corresponds with the score you give for the pain)



If you were to give a score from 0 – 10 for the average feeling of nausea that have experienced over the previous 8 hours what score would you give? (place an X on the line below to show the score you give)



If you were to give a score from 0 – 10 for the average degree of drowsiness (sleepiness) you have felt over the previous 8 hours, what score would you give? (place an X on the line below to show the score you give)



In the past 8 hours have you experienced any of the following at the ulcer site? (tick any relevant boxes)

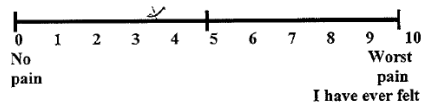
- ☐ Itching
☒ Burning
☐ Irritation
☐ Discomfort other than pain

Day 5

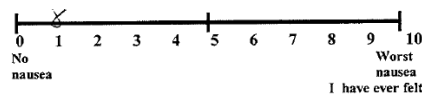
9am On average how intense has the pain been from the ulcer in the previous 8 hours? (tick the appropriate box)

- ☐ No pain
☐ Mild
☒ Moderate
☐ Severe
☐ Excruciating/very severe

If you were to give a score of 0 – 10 for the average intensity of pain that you have experienced from the ulcer in the past 8 hours what score would you give? (place an X on the line below that corresponds with the score you give for the pain)



If you were to give a score from 0 – 10 for the average feeling of nausea that have experienced over the previous 8 hours what score would you give? (place an X on the line below to show the score you give)



In the past 8 hours have you experienced any of the following at the ulcer site? (tick any relevant boxes)

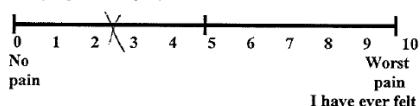
- ☐ Itching
☐ Burning
☐ Irritation
☒ Discomfort other than pain

Day 5

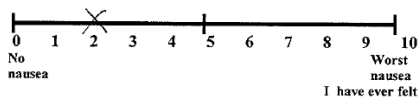
5pm On average how intense has the pain been from the ulcer in the previous 8 hours? (tick the appropriate box)

- ☐ No pain
☐ Mild
☒ Moderate
☐ Severe
☐ Excruciating/very severe

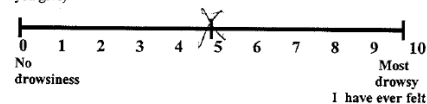
If you were to give a score of 0 – 10 for the average intensity of pain that you have experienced from the ulcer in the past 8 hours what score would you give? (place an X on the line below that corresponds with the score you give for the pain)



If you were to give a score from 0 – 10 for the average feeling of nausea that have experienced over the previous 8 hours what score would you give? (place an X on the line below to show the score you give)



If you were to give a score from 0 – 10 for the average degree of drowsiness (sleepiness) you have felt over the previous 8 hours, what score would you give? (place an X on the line below to show the score you give)



In the past 8 hours have you experienced any of the following at the ulcer site? (tick any relevant boxes)

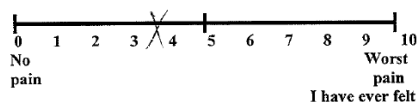
- ☐ Itching
☐ Burning
☐ Irritation
☒ Discomfort other than pain

Day 6

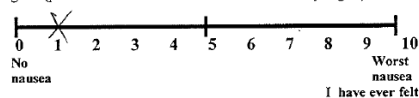
9am On average how intense has the pain been from the ulcer in the previous 8 hours? (tick the appropriate box)

- ☐ No pain
☐ Mild
☒ Moderate
☐ Severe
☐ Excruciating/very severe

If you were to give a score of 0 – 10 for the average intensity of pain that you have experienced from the ulcer in the past 8 hours what score would you give? (place an X on the line below that corresponds with the score you give for the pain)



If you were to give a score from 0 - 10 for the average feeling of nausea that have experienced over the previous 8 hours what score would you give? (place an X on the line below to show the score you give)



In the past 8 hours have you experienced any of the following at the ulcer site? (tick any relevant boxes)

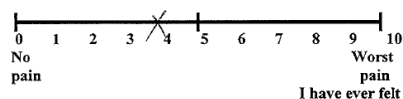
- ☐ Itching
☒ Burning
☐ Irritation
☒ Discomfort other than pain

Day 6

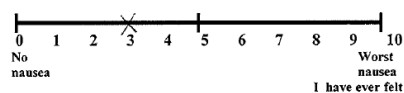
5pm On average how intense has the pain been from the ulcer in the previous 8 hours? (tick the appropriate box)

- ☐ No pain
☐ Mild
☒ Moderate
☐ Severe
☐ Excruciating/very severe

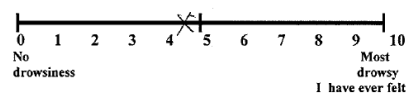
If you were to give a score of 0 – 10 for the average intensity of pain that you have experienced from the ulcer in the past 8 hours what score would you give? (place an X on the line below that corresponds with the score you give for the pain)



If you were to give a score from 0 - 10 for the average feeling of nausea that have experienced over the previous 8 hours what score would you give? (place an X on the line below to show the score you give)



If you were to give a score from 0 – 10 for the average degree of drowsiness (sleepiness) you have felt over the previous 8 hours, what score would you give? (place an X on the line below to show the score you give)



In the past 8 hours have you experienced any of the following at the ulcer site? (tick any relevant boxes)

- ☐ Itching
☐ Burning
☐ Irritation
☒ Discomfort other than pain

Day 7

9am On which days of this study did you experience the **least** amount of pain from the ulcer? (please tick box)

- ☒ Days 1&2
☐ Days 5&6
☐ no noticeable difference

15.7 RCT: Trial diary of patient number one

Topical morphine for painful Ulcers:
a randomised double blind placebo – controlled cross over trial

Trial diary

Patient Number:
 Trial Number: 1
 Start Date: 20/03/2002

PRE-TRIAL ASSESSMENT

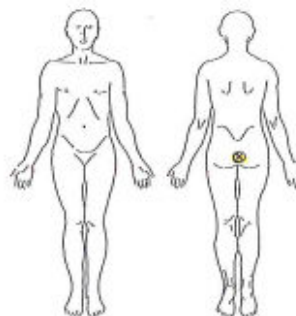
If the patient has ulcers on more than one site, only ONE site should be chosen and that site identified in the pre-assessment form. All other ulcers should be dressed in the appropriate manner.

Stirling grade classification

2.2

Nature of ulcer (please tick)

- ☒ Pressure ulcer
☐ Malignant ulcer
☐ Other (please specify ie arterial ulcer, venous ulcer)



Waterlow score [20]

Mattress: Key 2 Care Serene + Vicate Dry Air System Cushion

Grade	PATIENT'S ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours
③	Capable of only limited self care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair

----- FOR PATIENT TO COMPLETE -----

DATE 20.03.2002

Baseline Pre-Trial Assessment

If you were to give a score of 0 – 10 for the average intensity of pain that you have experienced from the ulcer in the past 24 hours what score would you give?

NO
PAIN

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

WORST PAIN
POSSIBLE

If you were to give a score from 0 - 10 for the average feeling of nausea that have experienced over the previous 24 hours what score would you give?

NO
NAUSEA

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

WORST NAUSEA
POSSIBLE

If you were to give a score from 0 – 10 for the average degree of drowsiness (sleepiness) you have felt over the previous 24 hours, what score would you give?

NO
DROWSINESS

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

WORST DROWSINESS
POSSIBLE

In the past 24 hours have you experienced any of the following at the ulcer site?
(tick any relevant boxes)

☐ Itching

☐ Burning

☐ Irritation

☐ Discomfort other than pain

----- FOR NURSING STAFF -----

Was there any pain on dressing the ulcer? yes [] no [✓]

Were any local reactions present? none [✓] allergic [] infection [] other []

Were any systemic side effects noted? no [✓] yes []

----- FOR NURSING STAFF AT DRESSING CHANGE (MORNING) -----

DAY 1. DATE: 21.03.2002

Was there any pain on dressing the ulcer? yes [] no [✓]

Were any local reactions present? none [✓] allergic [] infection [] other []

Were any systemic side effects noted? no [✓] yes []

----- FOR PATIENT TO COMPLETE (AFTERNOON)-----

If you were to give a score of 0 – 10 for the average intensity of pain that you have experienced from the ulcer since the last assessment, what score would you give?

NO
PAIN

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

WORST PAIN
POSSIBLE

If you were to give a score from 0 - 10 for the average feeling of nausea that have experienced since the last assessment, what score would you give?

NO
NAUSEA

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

WORST NAUSEA
POSSIBLE

If you were to give a score from 0 – 10 for the average degree of drowsiness (sleepiness) you have felt since the last assessment, what score would you give?

NO
DROWSINESS

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

WORST DROWSINESS
POSSIBLE

In the past 8 hours have you experienced any of the following at the ulcer site?
(tick any relevant boxes)

☐ Itching

☐ Burning

☐ Irritation

☐ Discomfort other than pain

FOR NURSING STAFF AT DRESSING CHANGE (MORNING) -----

DAY 2. DATE: 22nd March 202

Was there any pain on dressing the ulcer? yes [] no [✓]

Were any local reactions present? none [✓] allergic [] infection [] other []

Were any systemic side effects noted? no [✓] yes []

----- FOR PATIENT TO COMPLETE (AFTERNOON)-----

If you were to give a score of 0 – 10 for the average intensity of pain that you have experienced from the ulcer since the last assessment, what score would you give?

NO
PAIN

0	1	2	3	4	5	6	7	8	9	10
---	---	---	--------------	---	---	---	---	---	---	----

WORST PAIN
POSSIBLE

If you were to give a score from 0 - 10 for the average feeling of nausea that have experienced since the last assessment, what score would you give?

NO
NAUSEA

0	1	2	3	4	5	6	7	8	9	10
--------------	---	---	---	---	---	---	---	---	---	----

WORST NAUSEA
POSSIBLE

If you were to give a score from 0 – 10 for the average degree of drowsiness (sleepiness) you have felt since the last assessment, what score would you give?

NO
DROWSINESS

0	1	2	3	4	5	6	7	8	9	10
---	--------------	---	---	---	---	---	---	---	---	----

WORST DROWSINESS
POSSIBLE

In the past 8 hours have you experienced any of the following at the ulcer site?
(tick any relevant boxes)

☐ Itching

☐ Burning

☐ Irritation

☐ Discomfort other than pain

FOR NURSING STAFF AT DRESSING CHANGE (MORNING) -----

DAY 3. DATE: 23/03/03

Was there any pain on dressing the ulcer? yes [] no [✓]

Were any local reactions present? none [✓] allergic [] infection [] other []

Were any systemic side effects noted? no [✓] yes []

----- FOR PATIENT TO COMPLETE (AFTERNOON)-----

If you were to give a score of 0 – 10 for the average intensity of pain that you have experienced from the ulcer since the last assessment, what score would you give?

NO
PAIN

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

WORST PAIN
POSSIBLE

If you were to give a score from 0 - 10 for the average feeling of nausea that have experienced since the last assessment, what score would you give?

NO
NAUSEA

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

WORST NAUSEA
POSSIBLE

If you were to give a score from 0 – 10 for the average degree of drowsiness (sleepiness) you have felt since the last assessment, what score would you give?

NO
DROWSINESS

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

WORST DROWSINESS
POSSIBLE

In the past 8 hours have you experienced any of the following at the ulcer site?
(tick any relevant boxes)

☐ Itching

☐ Burning

☐ Irritation

☐ Discomfort other than pain

FOR NURSING STAFF AT DRESSING CHANGE (MORNING) -----

DAY 4. DATE: 24/03/02

Was there any pain on dressing the ulcer? yes [] no [✓]

Were any local reactions present? none [✓] allergic [] infection [] other []

Were any systemic side effects noted? no [✓] yes []

----- FOR PATIENT TO COMPLETE (AFTERNOON)-----

If you were to give a score of 0 – 10 for the average intensity of pain that you have experienced from the ulcer since the last assessment, what score would you give?

NO
PAIN

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

WORST PAIN
POSSIBLE

If you were to give a score from 0 - 10 for the average feeling of nausea that have experienced since the last assessment, what score would you give?

NO
NAUSEA

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

WORST NAUSEA
POSSIBLE

If you were to give a score from 0 – 10 for the average degree of drowsiness (sleepiness) you have felt since the last assessment, what score would you give?

NO
DROWSINESS

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

WORST DROWSINESS
POSSIBLE

In the past 8 hours have you experienced any of the following at the ulcer site?
(tick any relevant boxes)

☐ Itching

☐ Burning

☐ Irritation

☐ Discomfort other than pain

FOR NURSING STAFF AT DRESSING CHANGE (MORNING) -----

DAY 5. DATE: 25/02

Was there any pain on dressing the ulcer? yes [] no [☒]

Were any local reactions present? none [☒] allergic [] infection [] other []

Were any systemic side effects noted? no [☒] yes []

----- FOR PATIENT TO COMPLETE (AFTERNOON)-----

If you were to give a score of 0 – 10 for the average intensity of pain that you have experienced from the ulcer since the last assessment, what score would you give?

NO
PAIN

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

WORST PAIN
POSSIBLE

If you were to give a score from 0 - 10 for the average feeling of nausea that have experienced since the last assessment, what score would you give?

NO
NAUSEA

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

WORST NAUSEA
POSSIBLE

If you were to give a score from 0 – 10 for the average degree of drowsiness (sleepiness) you have felt since the last assessment, what score would you give?

NO
DROWSINESS

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

WORST DROWSINESS
POSSIBLE

In the past 8 hours have you experienced any of the following at the ulcer site?
(tick any relevant boxes)

☐ Itching

☐ Burning

☐ Irritation

☐ Discomfort other than pain

FOR NURSING STAFF AT DRESSING CHANGE (MORNING) -----

DAY 6. DATE: 24/5/05

Was there any pain on dressing the ulcer? yes [] no [x]

Were any local reactions present? none [x] allergic [] infection [] other []

Were any systemic side effects noted? no [x] yes []

----- FOR PATIENT TO COMPLETE (AFTERNOON)-----

If you were to give a score of 0 – 10 for the average intensity of pain that you have experienced from the ulcer since the last assessment, what score would you give?

NO
PAIN

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

WORST PAIN
POSSIBLE

If you were to give a score from 0 - 10 for the average feeling of nausea that have experienced since the last assessment, what score would you give?

NO
NAUSEA

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

WORST NAUSEA
POSSIBLE

If you were to give a score from 0 – 10 for the average degree of drowsiness (sleepiness) you have felt since the last assessment, what score would you give?

NO
DROWSINESS

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

WORST DROWSINESS
POSSIBLE

In the past 8 hours have you experienced any of the following at the ulcer site?
(tick any relevant boxes)

☐ Itching

☐ Burning

☐ Irritation

☐ Discomfort other than pain

And finally

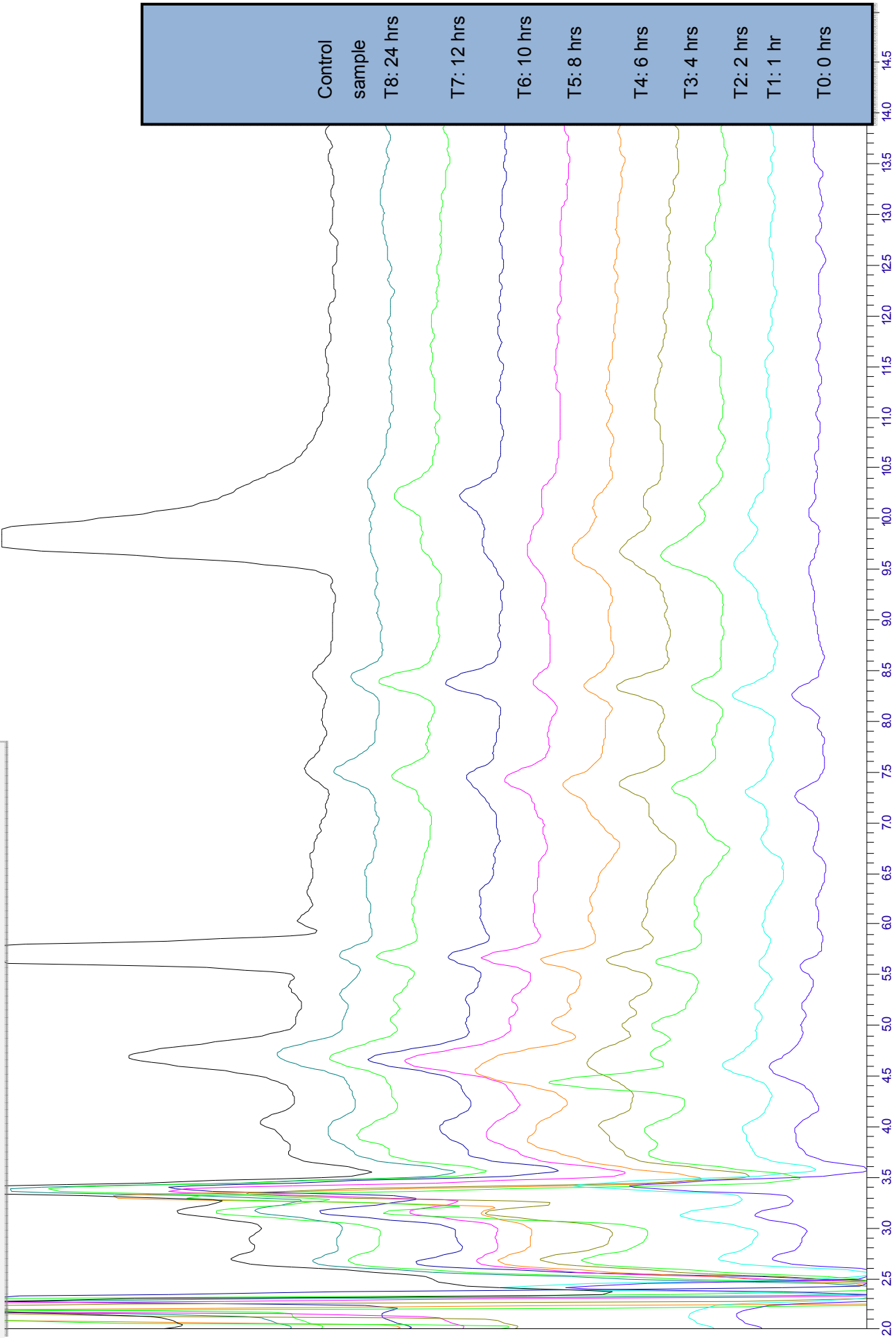
On which days of this study did you experience the least amount of pain from the ulcer?
(please tick box)

- ☒ Days 1&2
☐ Days 5&6
☐ no noticeable difference

Thank you

15.5 Patient bioavailability data following application of morphine to cutaneous ulcers

Bioavailability of topical morphine chromatogram: patient # 1

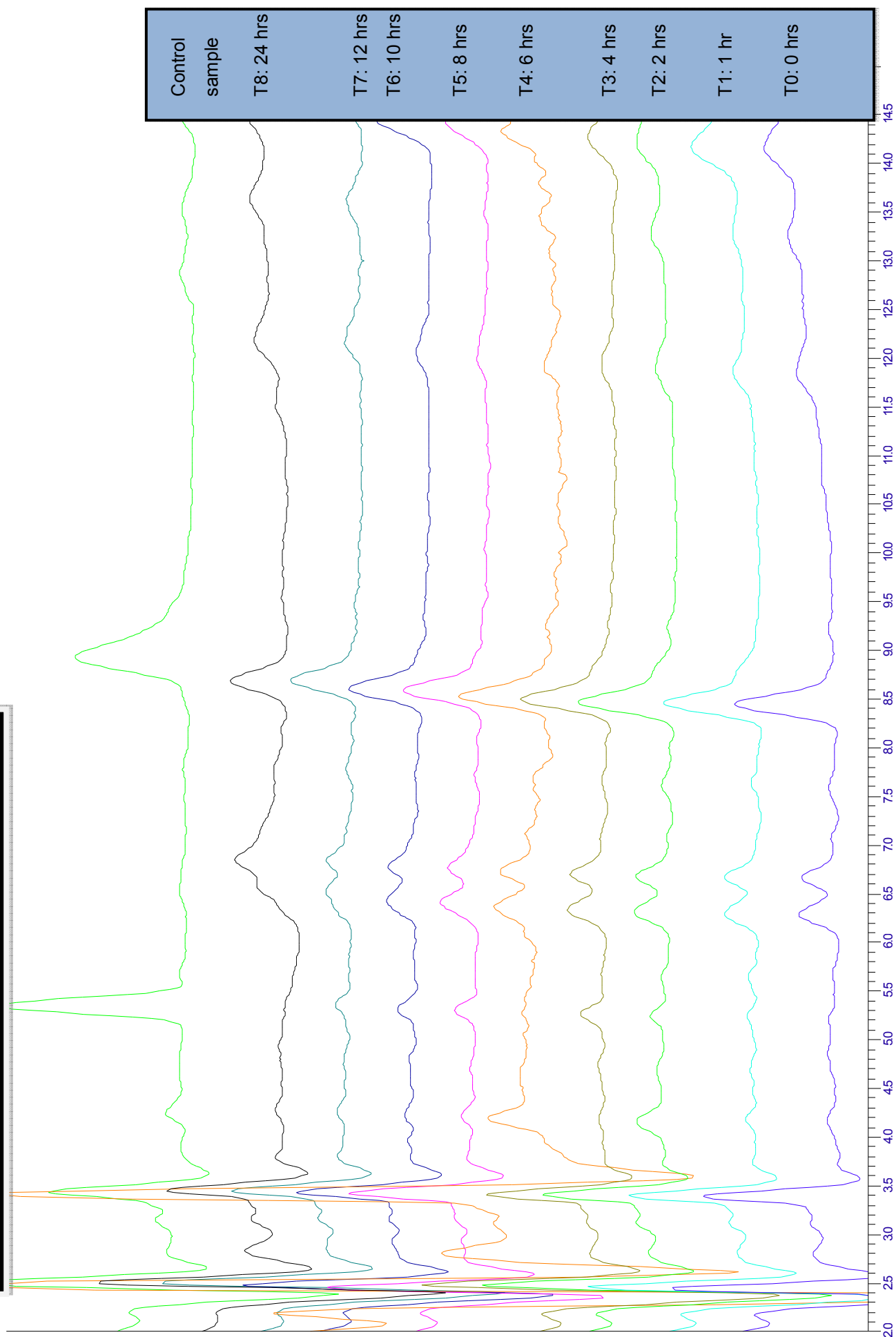


Bioavailability of topical morphine pharmacokinetic data: patient # 1

Patient 1	M3G [nm/l]	M6G [nm/l]	Morphine [nm/l]	Patient 1	M3G [nm/l]	M6G [nm/l]	Morphine [nm/l]
Top 0	<LLD	<LLD	<LLD	Top 0	<LLD	<LLD	<LLQ
Top 1	1.00	<LLD	<LLD	Top 1	1.00	<LLD	<LLQ
Top 2	2.00	<LLD	<LLD	Top 2	2.00	<LLD	<LLQ
Top 3	4.00	<LLD	<LLD	Top 3	4.00	<LLD	<LLQ
Top 4	5.00	<LLD	<LLD	Top 4	5.00	<LLD	<LLQ
Top 5	6.50	<LLD	<LLD	Top 5	6.50	<LLD	<LLQ
Top 6	8.00	<LLD	<LLD	Top 6	8.00	<LLD	<LLQ
Top 7	10.00	<LLD	<LLD	Top 7	10.00	<LLD	<LLQ
Top 8	24.00	<LLD	<LLD	Top 8	24.00	<LLD	<LLQ

	M3G [nm/l]	M6G [nm/l]	Morphine [nm/l]		M3G [nm/l]	M6G [nm/l]	Morphine [nm/l]
SC 0	<LLD	<LLD	<LLD	SC 0	#VALUE!	0.3	0.3
SC 1	1.00	<LLD	13.0	SC 1	1.00	1.5	13.0
SC 2	2.00	<LLD	33.0	SC 2	2.00	5.2	33.0
SC 3	4.00	187.2	87.9	SC 3	4.00	36.0	87.9
SC 4	6.00	256.0	73.3	SC 4	6.00	48.7	73.3
SC 5	8.00	257.2	62.8	SC 5	8.00	52.4	62.8
SC 6	10.00	297.4	48.3	SC 6	10.00	58.5	48.3
SC 7	12.00	212.3	19.5	SC 7	12.00	36.4	19.5
SC 8	24.00	190.8	14.6	SC 8	24.00	32.3	14.6

Bioavailability of topical morphine chromatogram: patient # 2

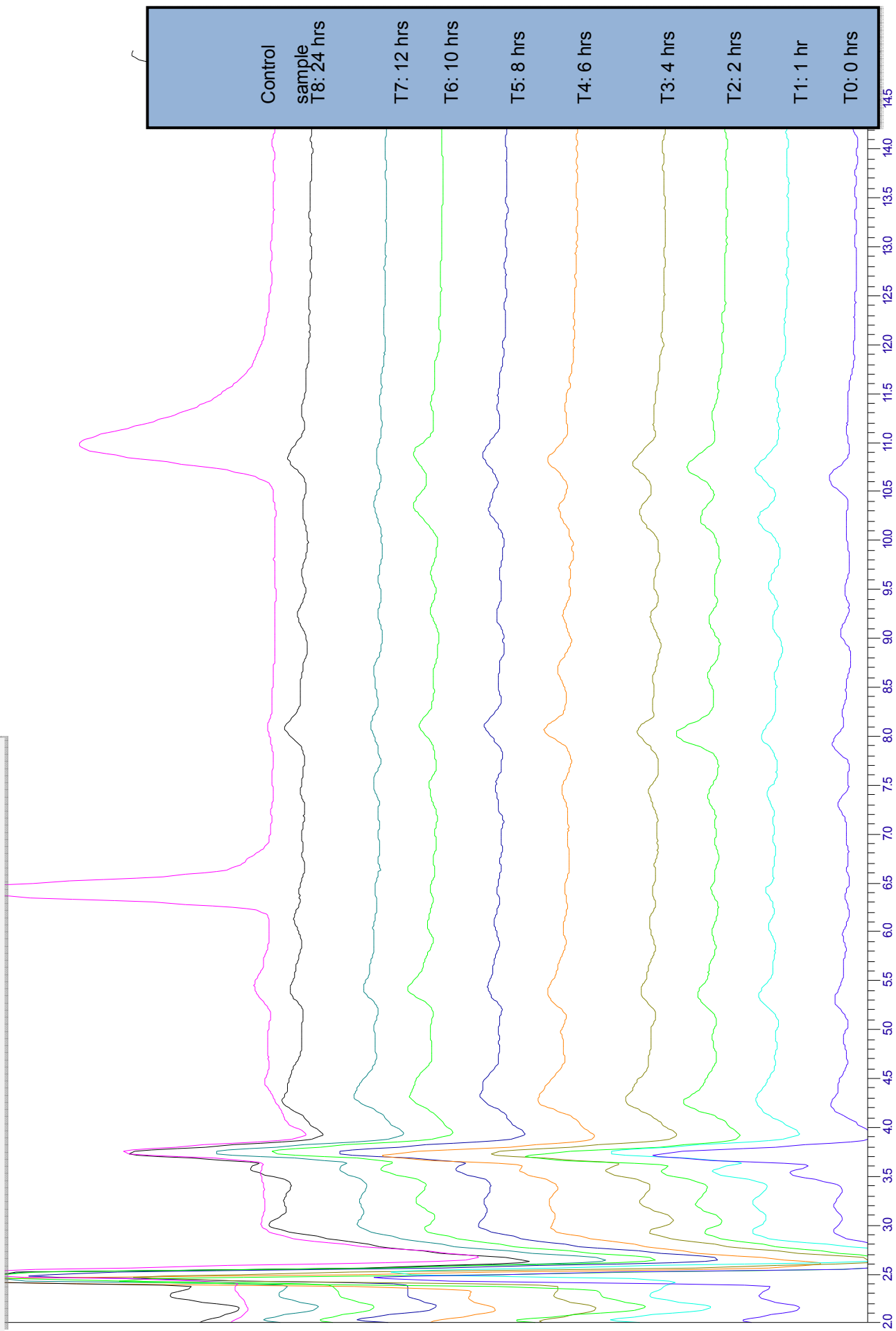


Bioavailability of topical morphine pharmacokinetic data: patient # 2

Patient 2	M3G [nm/I]	M6G [nm/I]	Morphine [nm/I]	Patient 2	M3G [nm/I]	M6G [nm/I]	Morphine [nm/I]
Top 0	<LLD	<LLD	<LLD	Top 0	<LLD	<LLD	<LLQ
Top 1	1.00	<LLD	<LLD	Top 1	1.00	<LLD	<LLQ
Top 2	2.00	<LLD	<LLD	Top 2	2.00	<LLD	<LLQ
Top 3	4.00	<LLD	<LLD	Top 3	4.00	<LLD	<LLQ
Top 4	6.00	<LLD	<LLD	Top 4	6.00	<LLD	<LLQ
Top 5	8.00	<LLD	<LLD	Top 5	8.00	<LLD	<LLQ
Top 6	10.00	<LLD	<LLD	Top 6	10.00	<LLD	<LLQ
Top 7	12.00	<LLD	<LLD	Top 7	12.00	<LLD	<LLQ
Top 8	24.00	<LLD	<LLD	Top 8	24.00	<LLD	<LLQ

	M3G [nm/I]	M6G [nm/I]	Morphine [nm/I]		M3G [nm/I]	M6G [nm/I]	Morphine [nm/I]
SC0	<LLD	2.6	<LLD	SC0	#VALUE!	2.6	#VALUE!
SC1	1.00	10.2	17.3	SC1	1.00	10.2	17.3
SC2	3.00	21.0	43.0	SC2	3.00	21.0	43.0
SC3	4.00	61.9	111.0	SC3	4.00	61.9	111.0
SC4	5.00	55.9	30.9	SC4	5.00	55.9	30.9
SC5	6.00	49.3	18.5	SC5	6.00	49.3	18.5
SC6	8.00	30.5	12.8	SC6	8.00	30.5	12.8
SC7	10.00	22.7	<LLD	SC7	10.00	22.7	2.5
SC8	12.00	17.2	<LLD	SC8	12.00	17.2	2.9

Bioavailability of topical morphine chromatogram: patient # 3

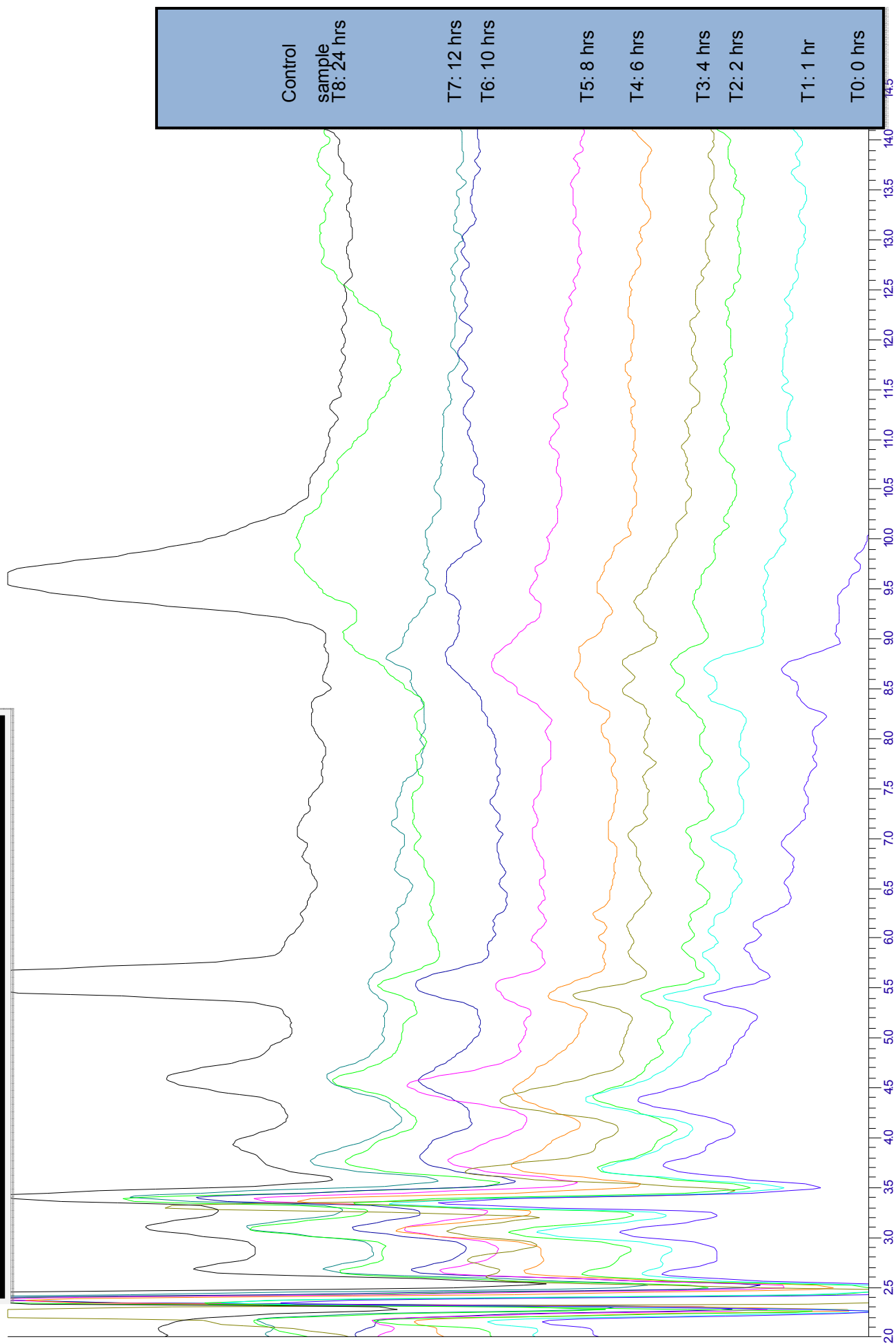


Bioavailability of topical morphine pharmacokinetic data: patient # 3

Patient 3	M3G [nm/I]	M6G [nm/I]	Morphine [nm/I]	Patient 3	M3G [nm/I]	M6G [nm/I]	Morphine [nm/I]
Top 0	<LLD	<LLD	<LLD	Top 0	<LLD	<LLD	<LLQ
Top 1	1.00	<LLD	<LLD	Top 1	1.00	<LLD	<LLQ
Top 2	2.00	<LLD	<LLD	Top 2	2.00	<LLD	<LLQ
Top 3	4.00	<LLD	<LLD	Top 3	4.00	<LLD	<LLQ
Top 4	6.00	<LLD	<LLD	Top 4	6.00	<LLD	<LLQ
Top 5	8.00	<LLD	<LLD	Top 5	8.00	<LLD	<LLQ
Top 6	10.00	<LLD	<LLD	Top 6	10.00	<LLD	<LLQ
Top 7	12.00	<LLD	<LLD	Top 7	12.00	<LLD	<LLQ
Top 8	24.00	<LLD	<LLD	Top 8	24.00	<LLD	<LLQ

	M3G [nm/I]	M6G [nm/I]	Morphine [nm/I]		M3G [nm/I]	M6G [nm/I]	Morphine [nm/I]
SC0	<LLD	<LLD	<LLD	SC0	#VALUE!	0.8	1.6
SC1	1.00	4.1	15.7	SC1	1.00	4.1	15.7
SC2	2.00	127.0	33.1	SC2	2.00	127.0	33.1
SC3	4.00	329.0	53.0	SC3	4.00	329.0	53.0
SC4	5.00	319.5	34.8	SC4	5.00	319.5	34.8
SC5	6.50	318.7	29.0	SC5	6.50	318.7	29.0
SC6	8.00	281.1	14.3	SC6	8.00	281.1	14.3
SC7	10.00	230.4	11.0	SC7	10.00	230.4	11.0
SC8	12.00	178.3	4.8	SC8	12.00	178.3	4.8

Bioavailability of topical morphine chromatogram: patient # 4

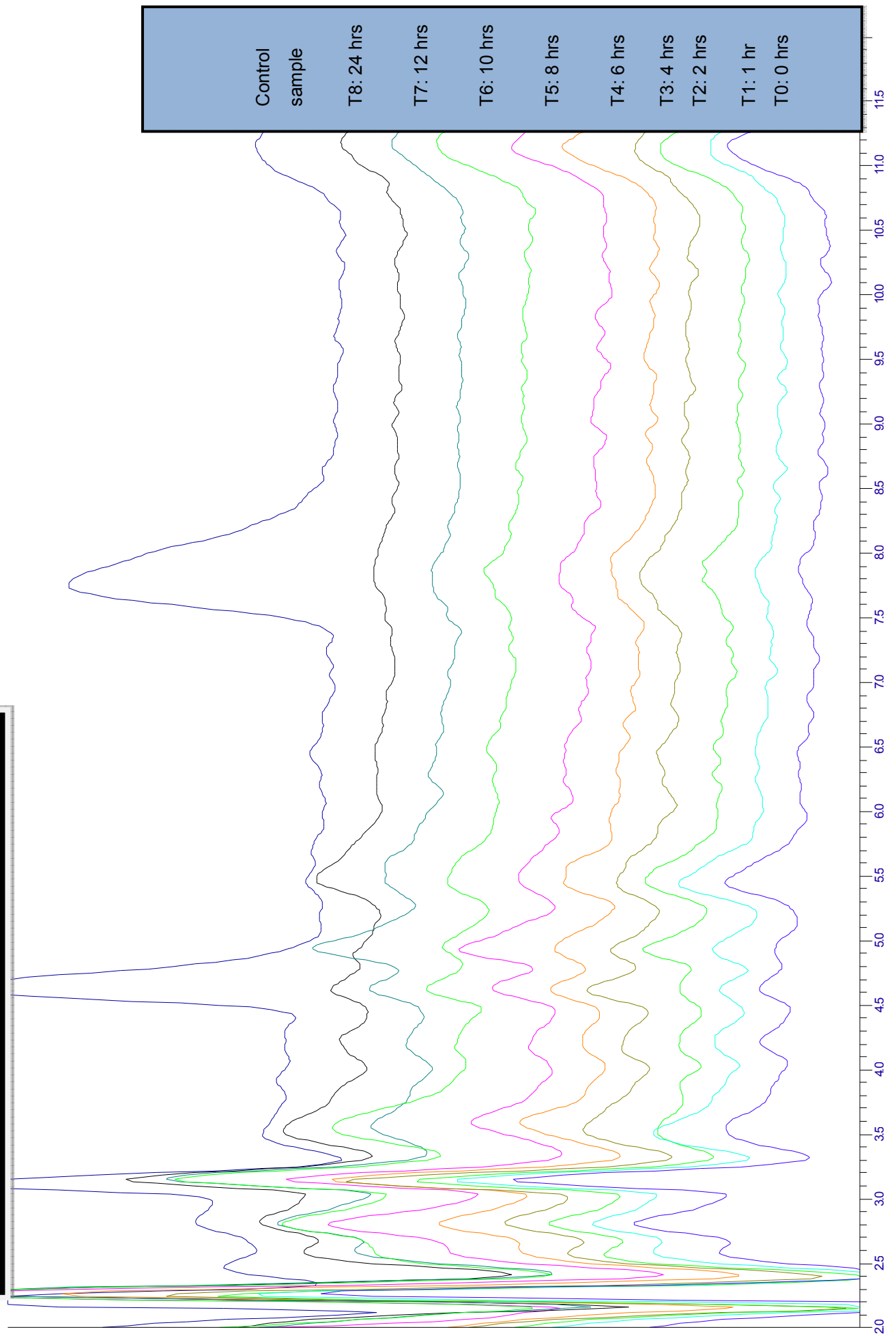


Bioavailability of topical morphine pharmacokinetic data: patient # 4

Patient 4	M3G [nm/l]	M6G [nm/l]	Morphine [nm/l]	Patient 4	M3G [nm/l]	M6G [nm/l]	Morphine [nm/l]
Top 0	<LLD	<LLD	<LLD	Top 0	<LLD	<LLD	<LLQ
Top 1	1.00	<LLD	<LLD	Top 1	1.00	<LLD	<LLQ
Top 2	2.00	<LLD	<LLD	Top 2	2.00	<LLD	<LLQ
Top 3	4.00	<LLD	<LLD	Top 3	4.00	<LLD	<LLQ
Top 4	5.00	<LLD	<LLD	Top 4	5.00	<LLD	<LLQ
Top 5	6.50	<LLD	<LLD	Top 5	6.50	<LLD	<LLQ
Top 6	8.00	<LLD	<LLD	Top 6	8.00	<LLD	<LLQ
Top 7	10.00	<LLD	<LLD	Top 7	10.00	<LLD	<LLQ
Top 8	24.00	<LLD	<LLD	Top 8	24.00	<LLD	<LLQ

	M3G [nm/l]	M6G [nm/l]	Morphine [nm/l]		M3G [nm/l]	M6G [nm/l]	Morphine [nm/l]
SC0	<LLD	<LLD	<LLD	SC0	0.0	0.8	0.6
SC1	1.00	<LLD	41.8	SC1	1.00	9.6	41.8
SC2	2.00	107.4	62.4	SC2	2.00	107.4	62.4
SC3	4.00	244.3	64.2	SC3	4.00	244.3	64.2
SC4	6.00	210.8	19.1	SC4	6.00	54.9	19.1
SC5	8.00	121.5	28.8	SC5	8.00	121.5	28.8
SC6	10.00	175.5	42.5	SC6	10.00	175.5	42.5
SC7	12.00	62.4	18.7	SC7	12.00	62.4	18.7
SC8	24.00	68.5	7.0	SC8	24.00	68.5	7.0

Bioavailability of topical morphine chromatogram: patient # 5

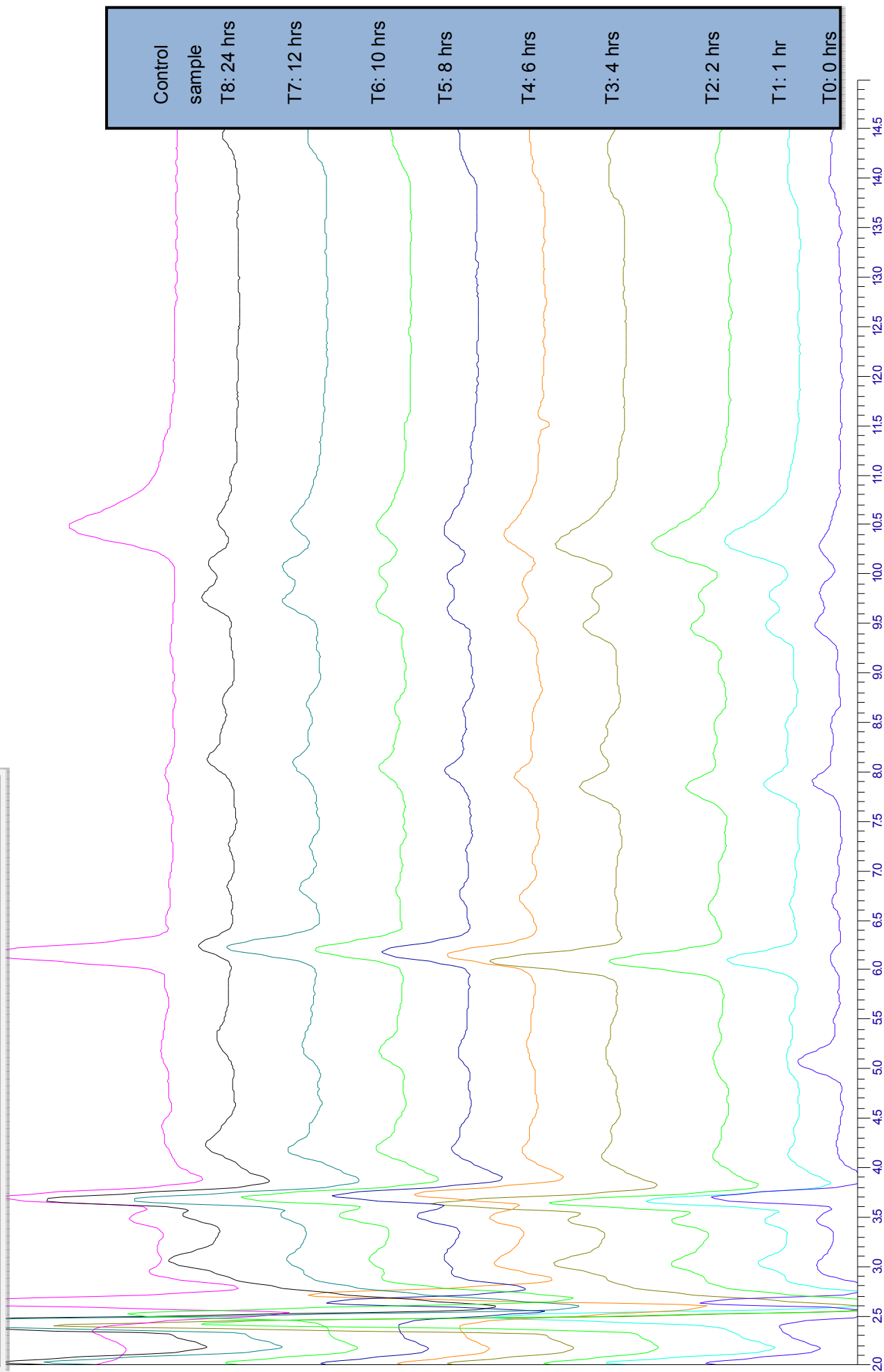


Bioavailability of topical morphine pharmacokinetic data: patient # 5

Patient 5	M3G [nm/I]	M6G [nm/I]	Morphine [nm/I]	Patient 5	M3G [nm/I]	M6G [nm/I]	Morphine [nm/I]
Top 0	<LLD	<LLD	<LLD	Top 0	<LLD	<LLD	<LLQ
Top 1	1.00	<LLD	<LLD	Top 1	1.00	<LLD	<LLQ
Top 2	2.00	<LLD	<LLD	Top 2	2.00	<LLD	<LLQ
Top 3	4.00	<LLD	<LLD	Top 3	4.00	<LLD	<LLQ
Top 4	5.00	<LLD	<LLD	Top 4	5.00	<LLD	<LLQ
Top 5	6.50	<LLD	<LLD	Top 5	6.50	<LLD	<LLQ
Top 6	8.00	<LLD	<LLD	Top 6	8.00	<LLD	<LLQ
Top 7	10.00	<LLD	<LLD	Top 7	10.00	<LLD	<LLQ
Top 8	23.50	<LLD	<LLD	Top 8	23.50	<LLD	<LLQ

	M3G [nm/I]	M6G [nm/I]	Morphine [nm/I]		M3G [nm/I]	M6G [nm/I]	Morphine [nm/I]
SC0	<LLD	<LLD	<LLD	SC0	#VALUE!	1.1	2.1
SC1	1.00	<LLD	23.8	SC1	1.00	5.2	23.8
SC2	2.00	199.2	52.4	SC2	2.00	32.1	52.4
SC3	4.00	348.2	62.7	SC3	4.00	70.1	62.7
SC4	5.25	292.5	27.8	SC4	5.25	70.9	27.8
SC5	6.00	305.8	25.9	SC5	6.00	71.4	25.9
SC6	8.00	260.6	13.4	SC6	8.00	49.7	13.4
SC7	10.00	123.3	8.0	SC7	10.00	32.9	8.0
SC8	12.00	212.3	5.2	SC8	12.00	26.3	5.2

Bioavailability of topical morphine chromatogram: patient # 6



Bioavailability of topical morphine pharmacokinetic data: patient # 6

Patient 6	M3G [nm/l]	M6G [nm/l]	Morphine [nm/l]	Patient 6	M3G [nm/l]	M6G [nm/l]	Morphine [nm/l]
Top 0	<LLD	<LLD	<LLD	Top 0	#VALUE!	0.8	1.9
Top 1	1.00	<LLD	9.4	Top 1	#VALUE!	5.3	9.4
Top 2	2.00	<LLD	8.5	Top 2	#VALUE!	7.5	8.5
Top 3	4.00	<LLD	7.4	Top 3	4.00	9.5	7.4
Top 4	6.00	<LLD	4.9	Top 4	6.00	7.3	4.9
Top 5	8.00	<LLD	3.3	Top 5	8.00	7.0	3.3
Top 6	10.00	<LLD	<LLD	Top 6	10.00	6.2	2.6
Top 7	12.00	<LLD	3.1	Top 7	#VALUE!	5.9	3.1
Top 8	24.00	<LLD	<LLD	Top 8	#VALUE!	1.5	1.3
	M3G [nm/l]	M6G [nm/l]	Morphine [nm/l]		M3G [nm/l]	M6G [nm/l]	Morphine [nm/l]
SC 0	<LLD	<LLD	<LLD	SC 0	#VALUE!	1.0	1.3
SC 1	1.00	<LLD	34.5	SC 1	#VALUE!	11.6	34.5
SC 2	2.00	141.6	56.5	SC 2	2.00	31.3	56.5
SC 3	4.00	274.4	50.9	SC 3	4.00	54.3	50.9
SC 4	5.00	288.4	30.3	SC 4	5.00	51.0	30.3
SC 5	6.50	240.0	15.2	SC 5	6.50	43.7	15.2
SC 6	8.00	211.2	10.7	SC 6	8.00	36.7	10.7
SC 7	10.00	149.6	5.3	SC 7	10.00	25.8	5.3
SC 8	12.00	111.9	3.2	SC 8	12.00	17.9	3.2